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CME MOC

Cleveland Clinic Journal of Medicine

Psychedelics in the medical toolbox?

Prolonged venous filling time and dependent rubor in peripheral artery disease

Should glucagon-like peptide 1 receptor agonists be withheld during the preoperative period?

New guideline on perioperative cardiovascular management before noncardiac surgery

Nociplastic pain: A practical guide to chronic pain management

Psychedelics, spirituality, and existential distress in patients at the end of life

Most elderly patients with subclinical hypothyroidism do not need to be treated

Subclinical hypothyroidism: What's in a name?

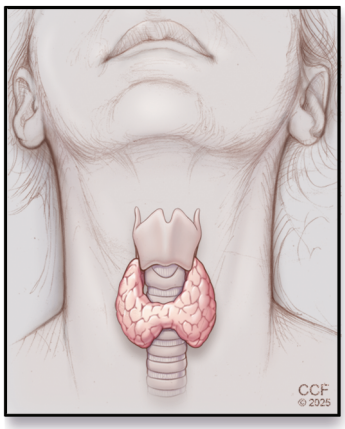

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Table of Contents

Upcoming Features

- Do I need to treat supine hypertension in my hospitalized patient?
- High-output heart failure from dialysis-associated arteriovenous access

Psychedelics in the medical toolbox?

*"Remember what the dormouse said, feed your head…"**

In this issue of the *Journal*, Cornish et al[1] discuss the potential therapeutic role of psychedelics in the care of patients at the end of life. This follows a previous paper[2] in the *Journal* in which a different group of authors discussed the use of psychedelics as an adjunctive component of psychotherapy in the treatment of various psychiatric conditions and substance use disorders. Given the historical association of psychedelics, including lysergic acid diethylamide (LSD), psilocybin, and mescaline, as "recreational" mind-altering, and possibly creativity-enhancing, compounds within countercultures of the 1960s and 1970s, their current introduction into several aspects of medical practice is a surprise to many. It may be even more of a surprise to those who recall news reports of "bad trips" linked to violent crimes or suicides in the past.

As I understand the rationale for psychedelics as a component of end-of-life care,[1] they have the potential to provide some relief to patients suffering from "existential distress." This distress can accompany a patient's confrontation with the immediacy of their mortality. Psychedelics may ease a patient's distress by providing an alternative coping and understanding pathway, using enhanced connectivity through vivid imagery reflecting their own thoughts as well as amplified responsiveness and interactions with persons around them. This seems consistent with experiences described by proponents of psychedelic use in the 1960s—that psychedelics can enhance introspection and promote a perception of oneness with a "true" reality, a component of enlightenment. The use of "mind-altering" chemicals or dramatic self-imposed physical interventions (eg, fasting, lodge sweating, sleep deprivation, meditation) in efforts to achieve a higher state of awareness and personal understanding has been a practice incorporated by many cultures and religions for centuries.

There are also some data demonstrating prolonged analgesic effects of LSD, comparable and, in some cases, superior to narcotics. But given the proclivity of many of us to passively ignore or actively deny our mortality throughout most of our lives, the use of psychedelics to dramatically confront and resolve our end-of-life issues may not be a good fit for everyone. The example case scenario in Cornish et al[1] presented a social worker (an occupation steeped in the need to confront emotional challenges head-on) who had previously self-experimented with psychedelics (thus likely eliminating the fear of the drug experience) is likely a better candidate than many for this therapeutic approach. There is recognition of the need in psychedelic-assisted therapy for the appropriate "set" (personal mindset) and environmental "setting" to increase the likelihood of therapeutic success, factors that can also complicate clinical trial design and interpretation.

Using the "mind-expanding" and sensory- and interaction-intensifying properties of psychedelics in this way fits with the personal use of these drugs in the 1960s and 1970s. Under controlled circumstances, I can see how their use can potentially facilitate the successful psychotherapeutic relationship[2]—providing the ability to engage with personal (and interpersonal) realities in a different and possibly enhanced manner. Assuming of course that the experience can be constrained within physically and emotionally safe environs, there may be accelerated therapeutic confrontation with deep-seated ("repressed") triggers for anxiety, depression, stress disorders, and on. But interestingly, the early use of psychedelics by psychiatrists was for a different intent.[3]

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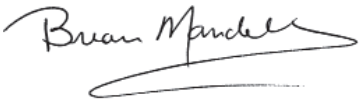
In the early 1900s, in part driven by stories from social anthropologists studying psychedelic use and consciousness-altering practices of various religious and cultural traditions, academic psychiatrists began to study the naturally occurring and later chemically synthesized psychedelics (LSD was synthesized by Albert Hoffman while working at Sandoz laboratories circa 1938). Experimentalists hoped to mimic defined psychiatric illnesses like schizophrenia by administering mescaline and other psychedelics to themselves and to healthy volunteers. Their goal was to mimic psychoses and thus support the concept of a biological basis for psychiatric illness, elevating the field of academic psychiatry to a level on par with the other scientifically advancing fields of medicine. Competing with these efforts was the work of Freud and other psychoanalysts.

There were several papers published detailing the biological, emotional, and cognitive effects of exposure to peyote, mescaline, and LSD. Synthesizing these data and the results of his own studies, British psychiatrist GT Stockings proposed that endogenous neurochemicals similar to mescaline were responsible for psychoses.[4] Experimentation with LSD continued through the 1960s, including studies attempting to relieve the psychological effects of war trauma by using psychedelics to have patients intensively relive their traumas in a controlled environment. Investigations of LSD continued until Sandoz Pharmaceuticals withdrew distribution of the compound, apparently in response to negative social pressures and rigid new restrictions on human drug experimentation enforced by the US Food and Drug Administration.

The biological basis for some psychiatric diseases was fully recognized when the Nobel Prize for Physiology or Medicine in 2000 was awarded to Arvid Carlsson for his discoveries concerning neurotransmitters, including his work elucidating the role of dopamine in the clinical expression of schizophrenia.

Grace Slick. "White Rabbit." On Jefferson Airplane recording Surrealistic Pillow. *Originally released in 1967.*



Brian F. Mandell, MD, PhD
Editor in Chief

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2025

APRIL

UPDATES IN PRIMARY IMMUNODEFICIENCY
April 4–5
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WELLNESS AND PREVENTIVE MEDICINE CONFERENCE
April 11
Beachwood, OH, and Live stream

THE NEW AGE OF ALZHEIMER'S DISEASE THERAPEUTICS
April 12
Live stream

NEPHROLOGY UPDATE
April 23–25
Cleveland, OH

PULSED FIELD ABLATION: CURRENT STATE AND FUTURE DIRECTIONS
April 24
San Diego, CA

INNOVATIONS IN NEUROSCIENCE
April 25
Avon, OH

ULTRASOUND COURSE: INTEGRATING POCUS INTO YOUR PRACTICE
April 30–May 3
Cleveland, OH

MAY

VASCULITIS 2025: ADVANCES AND CONTROVERSIES IN VASCULITIS
May 8
Cleveland, OH, and Live stream

BIOLOGIC THERAPIES SUMMIT
May 9–10
Cleveland, OH

DIABETES DAY
May 22
Cleveland, OH, and Live stream

PRIDE IN PRACTICE: STRATEGIES FOR LGBTQ+ INCLUSIVITY
May 30
Beachwood, OH

HEART OF THE CITY: CLEVELAND CLINIC HVTI CARDIOVASCULAR SYMPOSIUM
May 31
Hollywood, FL

JUNE

HEART FAILURE SUMMIT: EXPANDING THE FRONTIERS OF CONTEMPORARY TEAM MANAGEMENT
June 6–7
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 9–13
Live stream

INNOVATIONS IN CEREBROVASCULAR CARE
June 10–11
Cleveland, OH

MEDICAL ONCOLOGY UPDATE
June 18
Cleveland, OH

UPDATE IN MULTIPLE SCLEROSIS
June 20
Cleveland, OH, and Live stream

JULY

AI SUMMIT FOR HEALTHCARE PROFESSIONALS
July 11
Cleveland, OH, and Live stream

COACHING AND MENTORING ESSENTIALS FOR HEALTHCARE PROFESSIONALS
July 16–17
Live stream

CLEVELAND SPINE REVIEW COURSE
July 23–28
Cleveland, OH

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 1–3
Washington, DC

BREAST CANCER SUMMIT: COLLABORATING FOR A CURE
August 8
Cleveland, OH

MIDWEST MELANOMA SYMPOSIUM
August 15
Cleveland, OH

STATE OF THE ART TOPICS IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE
August 22–24
Cleveland, OH

SEPTEMBER

HOSPITAL MEDICINE SUMMIT
September 4–5
Cleveland, OH, and Live stream

COMPREHENSIVE LIFELONG EXPEDITIOUS CARE OF AORTIC DISEASE
September 12–13
Cleveland, OH

GLOBAL EP
September 12–13
Cleveland, OH

OCTOBER

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 3–5
Cleveland, OH, and Live stream

PRACTICAL MANAGEMENT OF STROKE
October 10
Warrensville Heights, OH

CARDIOVASCULAR UPDATE 2025 FOR PRIMARY CARE AND GENERAL CARDIOLOGY
October 16–17
Cleveland, OH

NOVEMBER

PRIMARY CARE + UPDATES IN PRIMARY CARE, WOMEN'S HEALTH AND BEHAVIORAL MEDICINE
November 12–15
Beachwood, OH

ADVANCING CARDIOVASCULAR CARE: CURRENT AND EVOLVING MANAGEMENT STRATEGIES
November 14
Columbus, OH

DECEMBER

MASTERING THE MANAGEMENT OF AORTIC VALVE DISEASE
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Prolonged venous filling time and dependent rubor in a patient with peripheral artery disease

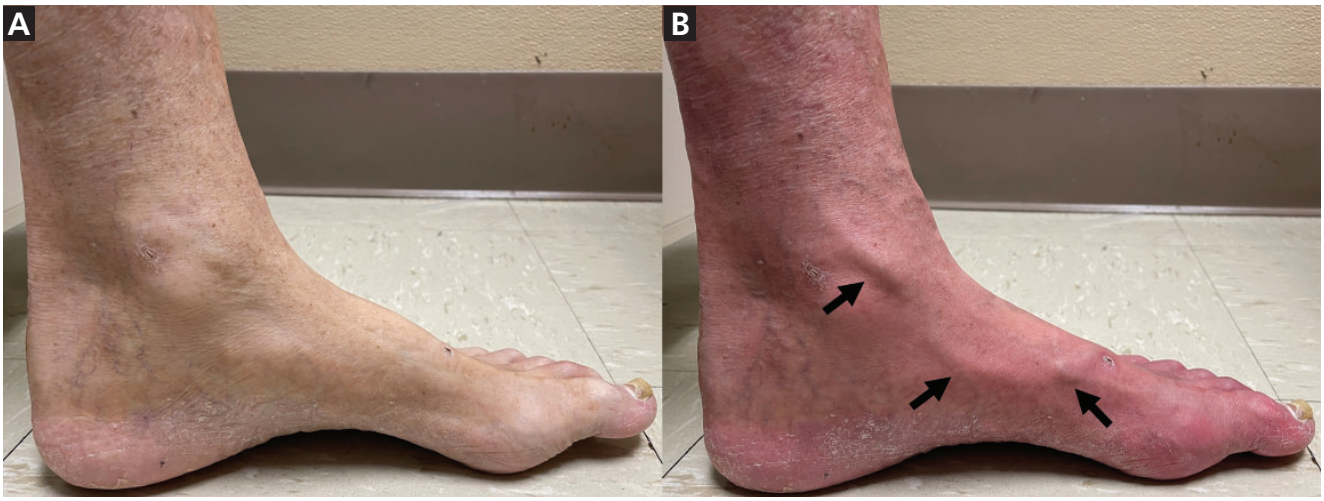

Figure 1. The patient's left leg was elevated 45 degrees above the examination table for 1 minute and then the patient was positioned sitting upright. (A) Elevation pallor was seen in the left foot immediately after the patient was repositioned sitting upright, and (B) 45 seconds later, the medial marginal vein of the left foot (black arrows) became visible and erythema of the entire foot was seen.

An 80-year-old man with a history of type 2 diabetes mellitus presented to the hospital with bilateral foot pain. Physical examination revealed absent bilateral posterior tibial and dorsalis pedis pulses and dusky erythema of both feet, which were cool to the touch. A prominent medial marginal vein on the left foot was identified (**Figure 1**), and the patient's leg was elevated to 45 degrees above the hospital bed surface for 1 minute. The patient was then positioned sitting upright. The erythema returned, and the duration of time for the vein to rise above the level of the skin surface was recorded (45 seconds). Additional findings were elevation pallor (foot appeared pale when elevated) and dependent rubor (foot appeared red when patient was standing), with erythema spreading proximally from the toes.

Because of concern for peripheral vascular disease, the patient was sent to the vascular laboratory for duplex ultrasonography to measure the ankle-brachial and toe-brachial indices. No definitive waveform in the posterior tibial artery was discernible, but the toe-brachial index of the left foot was 0.2 (normal value > 0.7). Computed tomography angiography subsequently revealed severe aortofemoral, femoropopliteal, and peroneotibial arterial disease.

doi:10.3949/ccjm.92a.24056

The patient was diagnosed with severe peripheral artery disease and referred for surgical revascularization.

THE ERYTHEMATOUS LOWER EXTREMITY

Erythematous lower extremities can present a diagnostic challenge.[1] Disorders on the differential diagnosis of an erythematous lower limb include cellulitis, peripheral artery disease, venous stasis dermatitis, asteatotic eczema (also called xerotic eczema or eczema craquelé), irritant or allergic contact dermatitis, gout, and erythromelalgia. Because atrophic skin changes and distal limb hair loss have poor sensitivity and specificity for the diagnosis of peripheral artery disease, other clinical signs discovered on careful physical examination are essential to establishing the diagnosis.[2,3]

Clinical evaluation

First, feel for warmth of the erythematous skin, as a cool extremity in an area of redness argues against cellulitis, gout, and erythromelalgia. Second, absence of pulsation in the femoral, popliteal, or posterior tibialis and dorsalis pedis arteries increases the likelihood of peripheral artery disease. After attempting to identify visible veins, such as the medial and lateral marginal veins of the foot, raise the affected extremity to 45 degrees above the examination table for 1 minute and observe for elevation pallor, which is suggestive of peripheral artery disease. Upon returning the patient to an upright position with the foot dangling, record the time for the previously identified visible vein to rise above the skin surface level and observe for the return of dependent rubor in the affected limb.

Venous filling time can be prolonged in peripheral artery disease because diminished arterial flow leads to slower filling of the veins in the affected area. A study of patients with diabetes found that a venous filling time longer than 20 seconds was the most specific (94%) examination finding for peripheral artery disease.[4] A prolonged venous filling time should *not* be observed in venous insufficiency because reflux into the lower leg veins causes rapid refilling of the veins. A normal or reduced venous filling time may be observed in patients with combined peripheral artery disease and venous insufficiency, which may explain the poor sensitivity (22%) of this measure if used alone to assess for peripheral artery disease.[4]

Dependent rubor is often present in severe peripheral artery disease due to reduced precapillary sphincter tone leading to passive dilation of the cutaneous capillary beds.

In summary, prolonged venous filling time is an indication of peripheral vascular disease with high specificity. In a patient with dependent rubor, its presence argues against the diagnosis of venous insufficiency.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should glucagon-like peptide 1 receptor agonists be withheld during the preoperative period?

A 58-year-old man with type 2 diabetes, a body mass index of 35 kg/m^2, and a history of recurrent right upper quadrant pain due to cholelithiasis is scheduled for elective laparoscopic cholecystectomy. His diabetes is well controlled with a glucagon-like peptide (GLP) 1 receptor agonist. Should GLP-1 receptor agonist therapy be withheld before the procedure? If so, when should it be discontinued?

A: Clinical judgment should guide decisions on whether to withhold GLP-1 receptor agonists before elective surgical procedures, taking into account patient symptoms, the presence of factors that increase risk for aspiration such as dysmotility disorders, and the clinical situation.

When discontinuing therapy, current clinical practice guidance from the American Society of Anesthesiologists recommends that GLP-1 receptor agonists be preoperatively withheld according to their dosing schedules, with daily administered agents withheld the day of the procedure and weekly administered agents withheld for 1 week before the procedure.[1]

WHY CONSIDER HOLDING GLP-1 RECEPTOR AGONISTS BEFORE SURGICAL PROCEDURES?

GLP-1 receptor agonists recapitulate the activity of the gut-derived hormone incretin, which is secreted at the time of food ingestion to help regulate blood glucose levels and satiety. GLP-1 receptor agonists delay gastric emptying, leading to concerns about retention of gastric contents even in patients who have followed fasting guidelines.[2] In addition, nausea and vomiting are common gastrointestinal side effects of GLP-1 receptor inhibitors, especially during the initiation phase of therapy or when they are taken at high doses. As such, patients taking GLP-1 receptor agonists may have an increased risk of aspiration of gastric contents during sedation and anesthesia.

The GLP-1 receptor agonists currently available in the United States have varying half-lives and observed delays in gastric emptying (**Table 1**).[2] GLP-1 receptor agonists with half-lives ranging from 5 to 7 days generally delay gastric emptying by 1 to 2 hours, whereas GLP-1 receptor agonists with half-lives ranging from 2 to 13 hours delay gastric emptying by 1 to 3 hours.

In a systematic review by Hiramoto et al,[3] solid-phase gastric emptying for patients taking GLP-1 receptor agonists was delayed by approximately 36 minutes (72% retention at 2 hours and 37% at 4 hours), although the clinical importance of this is unclear. Liquid-phase emptying was minimally affected, with no difference in acetaminophen absorption time between GLP-1 receptor agonist and placebo. These findings indicate a notable but not severe delay in solid-phase emptying, with liquid-phase emptying normalizing within 4 to 5 hours after ingestion.

WHAT FACTORS SHOULD INFORM THE DECISION TO HOLD GLP-1 RECEPTOR AGONISTS BEFORE AN ELECTIVE SURGICAL PROCEDURE?

Shared decision-making

The care team (surgical, anesthesiology, and prescribing clinicians) should use clinical judgment and evaluate the risks of GLP-1 receptor agonist administration well before a surgical procedure to allow time for adjustments. Such adjustments may include dietary changes or use of bridging medications if GLP-1 receptor agonist discontinuation is needed, although

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TABLE 1
Glucagon-like peptide 1 receptor agonists approved in the United States

Generic name	Administration route and frequency	Half-life	Gastric emptying delay
Dulaglutide	Subcutaneous injection weekly	5 days	120 minutes
Exenatide	Subcutaneous injection twice daily	2–3 hours	100–120 minutes
Exenatide, extended release	Subcutaneous injection weekly	8–14 days	144 minutes
Liraglutide	Subcutaneous injection daily	11–15 hours	70 minutes (median)
Semaglutide injection	Subcutaneous injection weekly	1 week	60 minutes
Semaglutide tablets	Oral daily	1 week	Unknown

Based on information from reference 2.

bridging may be resource intensive and increase risks such as hypoglycemia.[4]

Risks of discontinuing vs continuing

The decision to withhold GLP-1 receptor agonists before a procedure ultimately depends on the risk of aspiration vs the need for metabolic stability. Recent multisociety clinical practice guidance lists several factors that are considered to increase risk for delayed gastric emptying and aspiration perioperatively in patients taking GLP-1 receptor agonists[4]:

- Being in the dose-escalation phase of GLP-1 receptor agonist treatment
- Taking higher doses or weekly doses
- Having gastrointestinal symptoms of delayed gastric emptying (eg, nausea, vomiting, constipation)
- Having conditions that may delay gastric emptying, including gastroparesis and Parkinson disease.

The guidance notes that patients without these risk factors may continue GLP-1 receptor agonists before a surgical procedure.

The primary indication for GLP-1 receptor agonist therapy also may inform the decision of whether to withhold it preoperatively. For patients with obesity, in whom the risk of bronchoaspiration is higher, preoperative interruption of GLP-1 receptor agonist therapy may reduce residual gastric content and aspiration risk.[2] Note, however, that withholding of GLP-1 receptor agonists solely due to the presence of overweight or obesity, without a specific risk factor outlined above, may lead to bias against patients with these conditions.[4] For patients with type 2 diabetes, this decision should be individualized because of the risk of perioperative hyperglycemia and its association with poor outcomes.

Notably, discontinuing GLP-1 receptor agonists for patients with type 2 diabetes and cardiovascular disease may increase the risk of cardiac decompensation, worsening blood pressure and fluid retention and thereby exacerbating heart failure symptoms.[5] Reduced glycemic control and potential weight gain may also increase cardiac stress, while increased sympathetic activity and vascular stiffness may raise afterload, further straining the heart.

WHAT ARE RECOMMENDATIONS FOR HOLDING GLP-1 RECEPTOR AGONISTS BEFORE AN ELECTIVE SURGICAL PROCEDURE?

Guidance on duration of interruption

No evidence-based guidelines are currently available regarding how long GLP-1 receptor agonists should be interrupted during the preoperative period.[4,6] According to the American Society of Anesthesiologists consensus-based guidance on preoperative management of patients,[1] GLP-1 receptor agonists with daily dosing regimens should be withheld on the day of the procedure. GLP-1 receptor agonists with weekly dosing regimens should be withheld 1 week before the procedure. These recommendations apply regardless of the indication for GLP-1 receptor agonist use (ie, diabetes or weight loss), dose of GLP-1 receptor agonist, or procedure type.

Day-of-procedure guidance

If the patient has gastrointestinal tract symptoms (ie, nausea, vomiting, abdominal pain, or constipation) at the time of the procedure, the procedure should be delayed and the risk of aspiration discussed.[1] If the patient does not have gastrointestinal tract symptoms at the time of the procedure and has withheld GLP-1 receptor agonists for the recommended time, the procedure may be performed as planned. If the patient does not have gastrointestinal tract symptoms but has not withheld GLP-1 receptor agonist treatment according to recommendations, the procedure may be performed with *full stomach precautions*. These precautions include ensuring appropriate fasting (ie, 6 hours for solids and 2 hours for clear liquids), using rapid-sequence induction with cricoid pressure, administering antacids or

prokinetics, avoiding positive pressure ventilation, elevating the head, and delaying extubation until the patient is fully awake and can protect their airway.

If aspiration risk is a concern, point-of-care gastric ultrasonography should be used to assess stomach contents.[4] If the stomach is empty, the procedure may proceed as planned. For patients with confirmed gastric retention or a high risk of aspiration, rapid sequence induction and intubation should be considered to reduce aspiration risk and avoid canceling the procedure. American Society of Anesthesiologists practice guidelines[7] on fasting should be followed in all cases because of a lack of specific evidence for GLP-1 receptor agonist use.

GLP-1 receptor agonists may be restarted after the procedure is completed, although the optimal timing for restarting them is currently unclear and would vary based on the type of procedure performed.

WHAT ARE RECOMMENDATIONS FOR HOLDING GLP-1 RECEPTOR AGONISTS BEFORE AN ENDOSCOPIC PROCEDURE?

According to American Gastroenterological Association rapid clinical practice update on the management of patients taking GLP-1 receptor agonists prior to endoscopy,[8] GLP-1 receptor agonist use for diabetes management should be continued before endoscopy to maintain glycemic control. Gastrointestinal tract symptoms should be closely monitored. If no symptoms are apparent and fasting protocols are followed, the procedure may be performed as planned. For patients using GLP-1 receptor agonists for weight loss, withholding a dose before an endoscopic procedure should be considered, although this is not mandatory or evidence based.

If nausea or gastric retention is present the day of the procedure, further evaluation or management of these symptoms may be needed. For patients with serious gastrointestinal tract symptoms, transabdominal ultrasonography should be considered to assess gastric contents and determine whether the procedure should be delayed. Consuming a liquid diet the day before the procedure may be a safer alternative to stopping GLP-1 receptor agonist therapy.[8]

THE BOTTOM LINE

Patients at increased risk of aspiration who will undergo deep sedation or general anesthesia (especially those starting GLP-1 receptor agonist therapy or taking a high dose) may benefit from withholding GLP-1 receptor agonists.[4] For those who do not have an elevated risk of delayed gastric emptying and aspiration and are undergoing procedures with low aspiration risk (moderate sedation or local anesthesia), GLP-1 receptor agonist continuation may be safe. Strategies that may mitigate aspiration risks and allow continuation of GLP-1 receptor agonist therapy include a 24-hour preoperative clear liquid diet, rapid-sequence induction, or gastric ultrasonography to assess for retained gastric contents.

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2024 ACC/AHA guideline on perioperative cardiovascular management before noncardiac surgery: What's new?

ABSTRACT

In September 2024, the American College of Cardiology and American Heart Association updated their 2014 guidelines on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. This comprehensive document reinforces many previous recommendations and provides new evidence and expert opinion that is useful to the perioperative team, including information on risk assessment of ischemic heart disease and associated medical conditions, perioperative medications, cardiac devices, anesthesia, and monitoring. This overview summarizes the major concepts and changes in the new guidelines.

KEY POINTS

- The update reinforces a stepwise approach and proposes a modified algorithm for preoperative risk assessment and management.
- Like earlier guidelines, the update suggests preoperative cardiac tests be used judiciously, ie, only when the results will change management.
- Prophylactic revascularization is only indicated as it would be in the nonsurgical setting, ie, for acute coronary syndrome and left main coronary artery obstruction greater than 50%.
- The guidelines stress a multidisciplinary team–based approach that includes patient preferences.

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Very few patients undergoing noncardiac surgery need preoperative interventions such as coronary artery bypass grafting or percutaneous coronary intervention just to get them through surgery unless these procedures are otherwise indicated independent of the need for surgery. This has been an overriding theme of guidelines issued by the American College of Cardiology (ACC), American Heart Association (AHA), and several other professional organizations over the past 3 decades and continued in their latest version, issued in September 2024.[1]

This article highlights some of the key changes and recommendations of the new guidelines, how they differ from previous and other society guidelines, and ongoing challenges and unresolved issues facing physicians involved in perioperative care.

WHO WROTE THE GUIDELINES?

The original ACC/AHA guidelines for perioperative evaluation and management for noncardiac surgery were published in 1996 and updated in 2002, 2007, and 2014. In response to advances in preoperative evaluation and perioperative management for noncardiac surgery, the ACC and AHA in conjunction with several other cardiovascular societies updated the guidelines in 2024.[1]

WHAT ARE THE MAIN RECOMMENDATIONS?

The updated ACC/AHA guidelines[1] include the following recommendations:

For preoperative risk assessment

Use a stepwise approach. The new guidelines contain a new algorithm. **Figure 1** is a modification of this algorithm that also includes additional items related to a patient with previously undiagnosed or untreated coronary artery disease, prior revascularization, or recent cardiac test results.[2]

Determine timing and urgency of surgery. Definitions for timeframes to go to surgery were changed:

- *Emergency:* Previously meant the patient needed surgery within 6 hours; now it is less than 2 hours
- *Urgent:* Previously 6 to 24 hours; now 2 to 24 hours
- *Time-sensitive:* Previously 1 to 6 weeks; now up to 3 months
- *Elective:* Previously meant surgery could be delayed up to 1 year; now it means indefinitely.

Evaluate and treat unstable cardiac conditions. "Active cardiac conditions"—acute coronary syndrome, decompensated heart failure, and unstable arrhythmias—were included in the 2007 guidelines, removed from the 2014 algorithm (which was for coronary artery disease), but brought back in the 2024 guideline. Severe valvular heart disease was included in a new category of risk modifiers (see below). If the patient has one of these conditions, elective surgery should be postponed pending evaluation and treatment for these conditions.

Estimate risk of major adverse cardiac events. The guidelines recommend combining clinical and surgical risk factors and using a calculator to determine whether the patient is at low risk (< 1%) or elevated risk (≥ 1%). The Revised Cardiac Risk Index (RCRI), Myocardial Infarction or Cardiac Arrest (MICA), and American College of Surgeons Surgical Risk Calculator (ACS-SRC) were recommended in 2014, but the 2024 guidelines do not specify any particular calculator. Several others, including the American University of Beirut-HAS2 Risk Index, are listed.

Address risk modifiers. This is a new step, asking about diseases associated with increased risk that need to be evaluated but are not included in most risk calculators:

- Severe valvular heart disease
- Pulmonary hypertension
- Congenital heart disease
- Percutaneous coronary intervention or coronary artery bypass grafting
- Recent stroke
- Cardiac implantable electronic device
- Frailty.

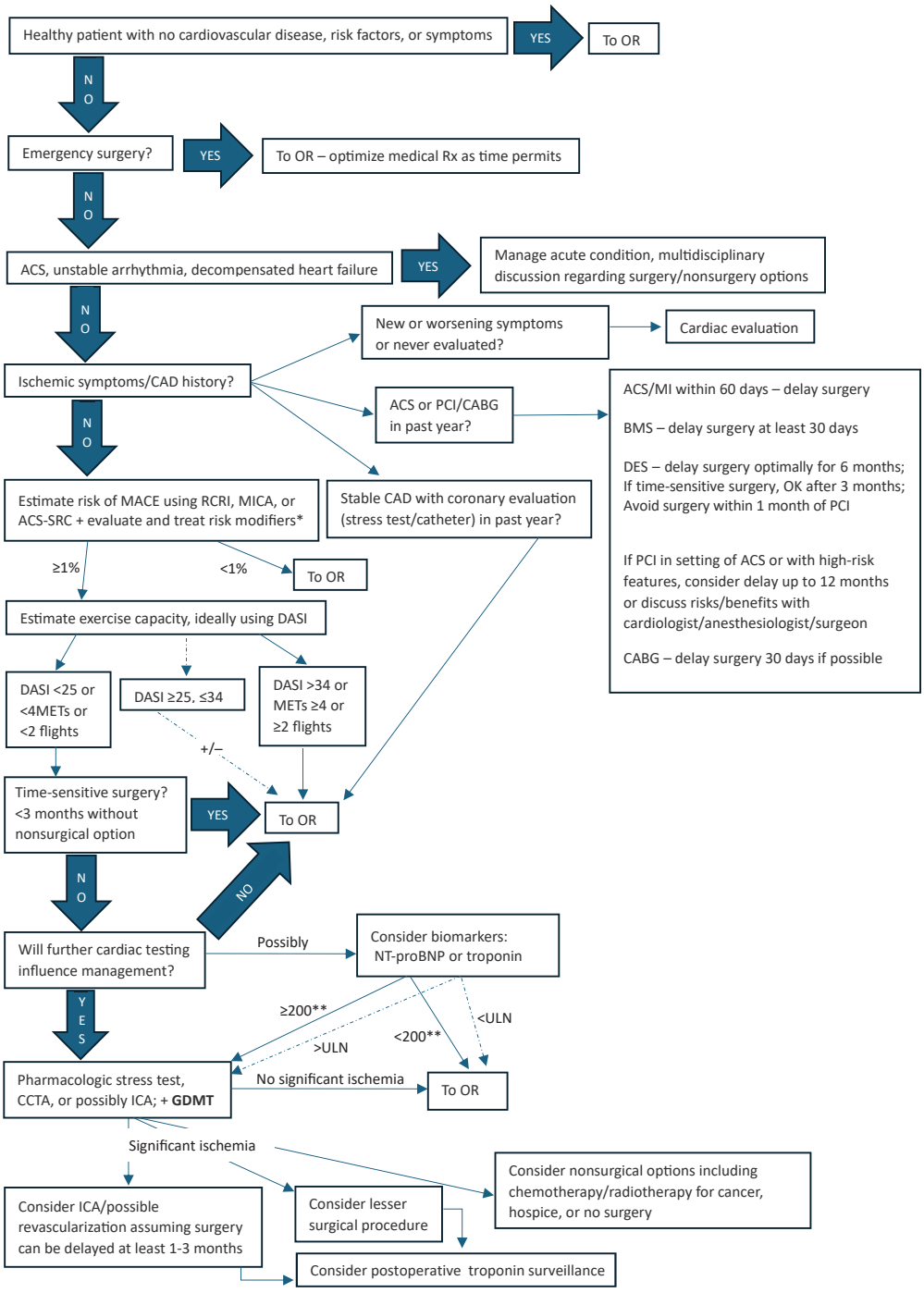
Assess functional status and exercise capacity. The algorithm still mentions a cutoff of 4 metabolic equivalents of task, below which a patient is considered to have poor functional capacity. However, how to accurately assess the patient's activity level has changed.

In the Measurement of Exercise Tolerance Before Surgery (METS) study,[3] clinician assessment of self-reported exercise capacity did not correlate with the number of metabolic equivalents achievable on cardiopulmonary exercise testing or predict postoperative complications, whereas a structured questionnaire—the Duke Activity Status Index (DASI)[4]—did predict complications. A DASI score higher than 34 (of a possible 58.2 points) was associated with low risk.[5] Because many patients have scores lower than 34, Fleisher, in a subsequent editorial,[6] suggested an option of using 25 points as another cutoff if you are willing to accept a slightly higher complication rate. Using the lower score as a cutoff would potentially avoid many unnecessary stress tests.

In contrast, data from the Basel Perioperative Myocardial Injury (Basel-PMI)[7] and the MET-Reevaluation for Perioperative Cardiac Risk (MET-REPAIR)[8] trials demonstrated that a patient's self-reported inability to climb 2 flights of stairs was associated with increased risk of postoperative cardiac complications and death. While this is noted in the text, it is not listed in the algorithm.

Consider using cardiac biomarkers. This is a new step in the algorithm. Natriuretic peptides (brain-type natriuretic peptide [BNP] or N-terminal pro–BNP [NT-proBNP]) or troponin may be considered for patients at elevated risk with poor exercise capacity going for elevated-risk noncardiac surgery to aid in the decision of whether to proceed to further cardiac testing. The ACC/AHA guidelines[1] prefer BNP or NT-proBNP, whereas the European Society of Cardiology[9] prefers troponin. If these values are normal (BNP < 92 ng/L, NT-proBNP < 300 ng/L as per the Canadian Cardiovascular Society guidelines[10] or possibly < 200 ng/L,[11] or troponin ≤ the 99th percentile for the assay), the patient is at low risk and no further cardiac testing is indicated. If these levels are elevated, the team needs to discuss whether to proceed with surgery, order further testing, or consider other options.

Order stress tests only if results will change management. This is one of the main themes of the



* Severe valvular disease, pulmonary hypertension, congenital heart disorder, cardiac implantable electronic device, recent stroke, frailty
** NT-proBNP cutoff is 300 ng/L in Canadian Cardiovascular Society guideline

Figure 1. CAD algorithm.

ACS = acute coronary syndrome; ACS-SRC = American College of Surgeons Surgical Risk Calculator; BMS = bare-metal stent; CABG = coronary artery bypass grafting; CAD = coronary artery disease; CCTA = computed tomography angiography; DASI = Duke Activity Status Index; DES = drug-eluting stent; GDMT = guideline-directed medical therapy; ICA = invasive coronary angiography; MACE = major adverse cardiac event; METs = metabolic equivalent of task; MI = myocardial infarction; MICA = Myocardial Infarction or Cardiac Arrest; NT-proBNP = N-terminal brain-type natriuretic peptide; OR = operating room; PCI = percutaneous coronary intervention; RCRI = Revised Cardiac Risk Index; Rx = prescriptions; ULN = upper limit of normal

guidelines. Stress testing is not indicated for patients at low risk, those going for low-risk surgery, or those with adequate exercise capacity. The guidelines recommend that stress tests be used judiciously, for the same indications as in the nonsurgical setting. If the results of further testing are significantly abnormal, once again a team discussion is necessary to decide whether to proceed to invasive coronary angiography and possible revascularization or consider a lesser surgical procedure, nonsurgical options, or not proceeding to surgery.

Consider monitoring troponin after surgery in patients at high risk. This is a change from the 2014 guidelines, which said troponin surveillance should be considered only in patients who had signs or symptoms of ischemia. Now if the patient is at high risk, postoperative troponins can be considered.

Prescribe guideline-directed medical therapy. Appropriate medical therapy to optimize the patient's medical status is emphasized at multiple steps in the algorithm.

Use a multidisciplinary team approach with shared decision-making. The guidelines emphasize the importance of communication and a team approach to decision-making.

For cardiac diseases other than coronary artery disease

Heart failure. Patients with heart failure are at increased risk of postoperative complications. Risk is higher still in those with heart failure with reduced ejection fraction and those with symptoms. Transthoracic echocardiography is indicated for new dyspnea or worsening symptoms, but not to routinely evaluate left ventricular function in patients without symptoms whose condition is clinically stable. Guideline-directed medical therapy should be continued perioperatively unless contraindicated. An exception is sodium-glucose cotransporter inhibitors, which should be withheld for 3 to 4 days before surgery in patients with heart failure to reduce the risk of perioperative metabolic acidosis.

Valvular heart disease. Transthoracic echocardiography is indicated for patients with known or suspected moderate-to-severe valvular heart disease. If a patient has no symptoms, their condition is clinically stable, and they have had an echocardiogram in the past year, it is not necessary to repeat it. Patients with severe valvular heart disease, in particular aortic stenosis, should be evaluated for possible valve replacement or repair before elective noncardiac surgery. If no intervention is indicated, they can proceed to surgery with appropriate monitoring and medical therapy.

Pulmonary hypertension and congenital heart disease. Management is complex and beyond the scope of this review. Consult a subspecialist.

Blood pressure. Continue most antihypertensive agents. If blood pressure is 180/110 mm Hg or higher before the day of surgery, consider delaying surgery until it is under better control. The anesthesiologist should maintain an intraoperative mean arterial pressure of at least 60 to 65 mm Hg or systolic blood pressure of at least 90 mm Hg.

Postoperative hypotension (mean arterial pressure < 60 or systolic blood pressure < 90 mm Hg) should be recognized and treated promptly.

Recommendations for perioperative medical management

Beta-blockers. Continue them if the patient is already taking them. If there is a new indication to start a beta-blocker (eg, ischemia on a stress test), start it at least 8 days before surgery to assess tolerability and dose titration, but do not start it on the day of surgery.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. If the patient has been taking these drugs chronically for hypertension and their blood pressure is controlled, withholding them 24 hours before surgery may limit intraoperative hypotension. If the patient takes them for heart failure with reduced ejection fraction, it is reasonable to continue them perioperatively.

Clonidine. Do not start it before surgery; however, continue it if the patient is already taking it to avoid rebound hypertension.

Statins. Continue statins in patients already taking them. If the patient is not already taking them, start them prophylactically for patients with an indication for them such as hyperlipidemia, diabetes mellitus, peripheral artery disease, or high 10-year cardiovascular risk.

Sodium-glucose cotransporter inhibitors. Withhold them 3 to 4 days (4 days for ertugliflozin) before surgery to minimize risk of euglycemic ketoacidosis.

Timing of noncardiac surgery after percutaneous coronary intervention

After balloon angioplasty without a stent, delay noncardiac surgery for at least 14 days.

After drug-eluting stent placement for acute coronary syndrome, elective noncardiac surgery should be delayed for at least 12 months. A 12-month delay between percutaneous coronary intervention and noncardiac surgery may also be appropriate for patients

undergoing complex drug-eluting stent placement (eg, bifurcation stents, long stent lengths, multivessel percutaneous coronary intervention). The European Society of Cardiology guidelines[9] say that patients have a high risk of perioperative stent thrombosis if they have any of the following: history of recurrent myocardial infarction, history of stent thrombosis under antiplatelet therapy, reduced left ventricular ejection fraction (< 40%), poorly controlled diabetes, severely impaired renal function or on hemodialysis, recent complex percutaneous coronary intervention (ie, severely calcified lesion, left main percutaneous coronary intervention, chronic total occlusion, bifurcational [crush] technique, bypass graft percutaneous coronary intervention), stent malapposition, or residual dissection.

After drug-eluting stent placement for chronic coronary disease, it is reasonable to delay elective noncardiac surgery for at least 6 months.

After drug-eluting stent placement, time-sensitive noncardiac surgery may be considered at least 3 months after percutaneous coronary intervention if the risk of delaying surgery outweighs the risk of perioperative major adverse cardiac events, and as early as 1 month after stent placement for chronic coronary disease in the European Society of Cardiology guidelines.[9]

After recent (≤ 30 days) placement of a bare-metal or drug-eluting stent, elective noncardiac surgery requiring interruption of 1 or more antiplatelet agents is harmful, posing a risk of stent thrombosis and ischemic complications.

Perioperative antiplatelet management after percutaneous coronary intervention

Continue aspirin perioperatively, if possible, considering bleeding risk and thrombotic risk, in all patients who have stents regardless of stent type or time of placement.

Continue dual antiplatelet therapy when possible if noncardiac surgery is required within 30 days of bare-metal stent or 3 months of drug-eluting stent placement.

In patients with prior percutaneous coronary intervention on oral anticoagulant monotherapy that must be stopped preoperatively, consider substituting aspirin until the oral anticoagulant can be resumed.

If antiplatelet drugs need to be stopped before surgery, stop prasugrel 7 days before, clopidogrel 5 days before, ticagrelor 3 days before, and aspirin 4 to 5 days before. Ticagrelor is the only reversible platelet inhibitor in this group.

Perioperative antiplatelet management with no prior percutaneous coronary intervention

If the patient is taking aspirin for secondary prevention (because of chronic coronary disease, prior myocardial infarction, or cerebrovascular accident), it may be reasonable to continue it if the risk of cardiac events outweighs the risk of bleeding.

If the patient is taking aspirin for primary prevention and not undergoing carotid surgery, it should be discontinued. If not on aspirin in these settings, initiation of aspirin preoperatively is not indicated.

Bridging anticoagulation

Patients on warfarin. In patients with cardiovascular disease and high thrombotic risk who need to interrupt their vitamin K antagonist (eg, warfarin), preoperative bridging with parenteral heparin (usually low-molecular-weight heparin) can be used. Periprocedural bridging is not indicated in most patients due to increased risk of bleeding.

Patients on direct-acting oral anticoagulants. Patients who need to stop a direct-acting oral anticoagulant preoperatively do not require bridging because these drugs have shorter half-lives than warfarin, and therefore the patient will be without full anticoagulation for a shorter time.

Other recommendations

The guidelines provide recommendations for preoperative management of blood glucose, anemia, sleep apnea, stroke, type of anesthesia, tranexamic acid, cardiac implantable electronic devices, pulmonary artery catheters, transesophageal echocardiography, and body temperature, as well as pain management, postoperative atrial fibrillation, and management of myocardial injury after noncardiac surgery, but it is beyond the scope of this review to discuss them.

WHAT IS DIFFERENT FROM PRIOR GUIDELINES?

The updated guidelines[1] differ from previous versions on the following points:

- Differences in definitions of urgency and timing of surgery
- Use of a structured questionnaire or stair climbing to assess exercise capacity
- Inclusion of risk modifiers
- Use of biomarkers to aid in decision-making for further cardiac tests
- Consideration of coronary computed tomography angiography as an alternative to pharmacologic stress testing
- Specific recommendations for revascularization

before surgery, ie, acute coronary syndrome and greater than 50% occlusion of the left main coronary artery
- Consideration of postoperative troponin surveillance in patients at high risk
- Medication management recommendations.

DO OTHER SOCIETIES AGREE OR DISAGREE?

The 2022 European Society of Cardiology guidelines[9] are similar in many ways to the ACC/AHA ones,[1] but they are more liberal in their recommendations for transthoracic echocardiography and stress tests. They also prefer preoperative troponin measurements rather than natriuretic peptides, whereas the ACC/AHA guidelines prefer natriuretic peptides. They also note that after percutaneous coronary intervention, a patient can proceed to time-sensitive surgery after just 1 month of dual antiplatelet therapy, as opposed to 3 months in the ACC/AHA guidelines.

The 2017 Canadian Cardiovascular Society guidelines[10] are very different from the ACC/AHA and European Society of Cardiology guidelines in that they specify using the Revised Cardiac Risk Index as the only validated calculator, recommend using preoperative BNP and NT-proBNP measurements as well as postoperative troponin and electrocardiograms for patients at increased risk, not recommending any cardiac tests (transthoracic echocardiography or stress tests), and withholding angiotensin-converting enzyme inhibitor and angiotensin receptor blocker medications at least 24 hours before surgery for all patients.

WHEN WOULD THE GUIDELINES NOT APPLY?

The 2024 ACC/AHA guidelines provide a framework to assist clinicians with cardiac evaluation and management for patients undergoing noncardiac surgery. However, they cannot address all clinical scenarios and nuances. For example, urgency of the surgery may force the clinician to deviate from standard treatment protocols, and high bleeding risks may result in stopping antiplatelet therapy despite recommendations to continue it. Decisions need to be individualized, with the guidelines serving as the main clinical support tool.

Additionally, many of the ACC/AHA recommendations are class 2, meaning that something *may* be considered or may be reasonable, giving the clinician the option to do something or not. Clinical experience and discussion with the surgical team and patient play a role in these decisions.

WHAT IS THE EXPECTED CLINICAL IMPACT?

The updated ACC/AHA guidelines provide a streamlined approach to the management of the patient undergoing noncardiac surgery. For those clinicians following the perioperative literature who have already incorporated data from various clinical trials since 2014, the new guidelines will most likely reinforce their practice. However, for those who were using the 2014 guidelines and unaware of newer studies, the updated algorithm represents a major change in terms of evaluating exercise capacity, using preoperative biomarkers, and considering postoperative troponin surveillance. They also update the timing of surgery after percutaneous coronary intervention and management of antiplatelet therapy.

HOW WILL THIS CHANGE DAILY PRACTICE?

Following a stepwise approach, using a more structured questionnaire, and incorporating cardiac biomarkers in decision-making will hopefully lead to better risk assessment and minimize unnecessary stress tests. Appropriate medication management, careful attention to and treatment of hypotension, and vigilant postoperative monitoring and follow-up may improve outcomes. Incorporation of artificial intelligence and machine-learning may improve risk assessment, but future studies are needed to evaluate risk-reduction strategies.

DISCLOSURES

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REVIEW

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Most elderly patients with subclinical hypothyroidism do not need to be treated

ABSTRACT

Whether subclinical hypothyroidism should be treated in elderly patients (≥ 65 years) is controversial. The authors argue for a personalized, wait-and-see approach rather than universal treatment, pointing out that randomized clinical trials have not shown that levothyroxine treatment makes any difference in terms of hard clinical end points, quality of life, or hypothyroid symptom relief in elderly patients with this condition.

KEY POINTS

- Subclinical hypothyroidism is categorized as either mild (grade 1; thyroid-stimulating hormone [TSH] level 4.0–10.0 mIU/L) or severe (grade 2; TSH > 10 mIU/L).
- High TSH levels in patients older than 65 years may be due to aging and do not necessarily require treatment.
- The French Endocrine Society proposes using the patient's age divided by 10 as the upper limit of normal for TSH (in mIU/L) when screening and following elderly patients.
- Studies have not found levothyroxine replacement therapy to make any significant clinical difference in most cases of mild subclinical hypothyroidism in older patients. However, lack of consistent age-appropriate TSH screening methods limits definitive conclusions.
- In most mild cases, TSH can be remeasured 2 to 3 months after diagnosis. Treatment decisions are individualized, and potential risks and benefits must be considered.

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Most patients with subclinical hypothyroidism do not need to be treated for it, and for many, it may be a normal part of aging and can be monitored without active intervention.

The US Preventive Services Task Force defines subclinical hypothyroidism as an elevated serum thyrotropin (thyroid-stimulating hormone, TSH) level (> 4.50 mIU/L), but with a normal free thyroxine (T4) level.[1] Despite the term *subclinical*, symptoms may or may not be present, although they tend to be mild and nonspecific.

See related article page 233

Guidelines for diagnosing and managing *overt* hypothyroidism (in which the TSH level is elevated and the T4 level is low) enjoy broad consensus.[2,3] However, whether to treat subclinical hypothyroidism is controversial, especially in people 65 and older. A host of factors, including age, can affect TSH levels. Adding to the challenge, the ideal TSH cutoff point for initiating treatment remains a topic of debate.[4] Mildly elevated TSH does not necessarily lead to long-term adverse consequences, and overtreatment can increase the risks of fractures, cardiovascular disease, and dysrhythmias.[5]

Here, we review the challenges of managing subclinical hypothyroidism in the elderly (age 65 and older) and argue against routinely treating it with levothyroxine in this age group. We do not cover how to manage it in younger adults, women of childbearing age, or children.

TABLE 1
Advantages and disadvantages of different thyroid function tests

Test	Advantages	Disadvantages	Preferred use
Thyrotropin (thyroid-stimulating hormone, TSH)[7]	Sensitive to changes in thyroid hormone levels Useful in diagnosing primary and secondary hypothyroidism	Can be influenced by nonthyroid factors (eg, illness, medications)	Primary test for diagnosing hypothyroidism and monitoring thyroid hormone replacement therapy
Free thyroxine (T4)[2,8]	More accurate reflection of thyroid hormone levels than total T4, less influenced by changes in binding proteins	Can be affected by protein-binding changes, especially in certain conditions (eg, pregnancy, liver disease)	Essential for assessing thyroid hormone status, especially in conditions affecting thyroid-binding proteins
Free triiodothyronine (T3)[7,9]	More accurate reflection of thyroid hormone activity than total T3, less influenced by changes in binding proteins	Lower concentration, weaker protein binding, less precise measurement Often normal in early and mild hypothyroidism due to mostly peripheral conversion, especially in early hypothyroidism	Consider in specific clinical scenarios, such as suspected nonthyroid illness syndrome or hyperthyroidism
Thyroglobulin	Elevated levels may indicate residual or recurrent thyroid cancer	Can be affected by thyroid inflammation and other factors	Used in the management of patients with thyroid cancer
Thyroid peroxidase antibodies	Positive test suggests autoimmune thyroiditis; often associated with Hashimoto thyroiditis	Not specific—can be positive in other autoimmune conditions	Used in the diagnosis and management of autoimmune thyroid diseases

PRIMARILY A LABORATORY DIAGNOSIS

The clinical presentation of hypothyroidism often deviates from the classic textbook description. Carlé et al[6] report that tiredness is the most important symptom of overt hypothyroidism. However, many patients with subclinical hypothyroidism experience no symptoms or only nonspecific symptoms. Consequently, subclinical hypothyroidism is primarily a biochemical or laboratory diagnosis.

TSH is more sensitive than T4

TSH levels have a log-linear inverse relationship with T4 and triiodothyronine (T3) levels, so that a 2-fold decrease in T4 results in a 100-fold increase in TSH.[7] Therefore, TSH is more sensitive to changes in thyroid function.

Free T4 measurements, complementing TSH, help classify hypothyroidism as overt or subclinical and determine the need for treatment. Free T4 is a better marker of hormone action than total T4, as the latter is 99.97% bound to proteins (thyroid-binding globulin, transthyretin, prealbumin, and albumin), and conditions that alter these binding proteins affect the accuracy of total T4 measurements.[8] Also, unbound (free) T4 is the biologically active fraction and is widely accepted as a better activity marker.[2]

T3 is 99.7% protein-bound, and the free T3 level (the other 0.3%) is theorized to be a better marker than total T3. However, free T3 has a lower concentration than free T4 and a weaker affinity for protein carriers, which renders it more susceptible to free fatty acids (which inhibit its binding to its receptor) and drug interactions.[9] Consequently, the precision and reproducibility of free T3 measurements are less ideal than those of free T4. Also, T3 levels tend to be within reference ranges in cases of suspected hypothyroidism or elevated TSH and so have limited clinical value (**Table 1**).[2,7–9] As a result, in the special cases in which T3 measurements are needed, such as euthyroid sick syndrome, many laboratories prefer total T3 assays rather than free T3.

The American[2,3] and European thyroid associations[10] classify subclinical hypothyroidism as either mild (grade 1) or severe (grade 2) based on the TSH

level (**Table 2**)—about 90% of patients with subclinical hypothyroidism have TSH levels of 10 mIU/L or lower (ie, mild or grade 1).

Before diagnosing subclinical hypothyroidism, one must make sure the thyroid function has been stable for at least several weeks to exclude transient changes caused by nonthyroidal illness, thyroiditis, or medications.[2] We remeasure TSH 2 to 3 months after the first measurement.

COMMON IN THE ELDERLY

Western countries are getting older. Consequently, the prevalence of subclinical hypothyroidism is also rising, reflecting the growing proportion of the population at risk.[11]

In the third National Health and Nutrition Examination Survey (NHANES III),[12] in people age 12 years and older in the United States, the prevalence of subclinical hypothyroidism was 4.3% and the prevalence of overt hypothyroidism, characterized by low free T4 levels, was 0.3%. In the Cardiovascular Health Study,[13] in participants age 65 and older, the prevalence of subclinical hypothyroidism was 15%, and it was higher in women than in men.

MANY FACTORS AFFECT TSH LEVELS

When T4 and T3 levels are low, the pituitary gland releases TSH to increase thyroid hormone production, whereas high T4 and T3 levels inhibit TSH release. However, many other factors can affect the TSH level, making abnormal values difficult to interpret (**Table 3**).[14–21] TSH levels are not static but fluctuate within individuals over time,[17] owing to a range of factors:

- **Circadian rhythm.** TSH levels peak in the early morning hours and then decline, reaching a trough in the early afternoon and evening
- **Pulsatile secretion.** TSH is secreted in pulses, contributing to further fluctuations
- **Season.** Levels are generally higher in winter and lower in summer
- **Age.** TSH levels mildly increase with age, and elevations may be normal for some individuals[12,18]
- **Other factors,** which include inconsistencies in testing methods, thyroid antibodies and thyroid hormone resistance,[11,19,20] silent or granulomatous thyroiditis, and certain medications.[21]

Genetic differences also affect thyroid hormone levels, so that some patients whose TSH levels are within the normal range can have symptoms while others with slightly elevated TSH might not.[22] Also, iodine intake varies in geographic regions.

TABLE 2
Classification of subclinical hypothyroidism

	Thyroid-stimulating hormone range (mIU/L)	Free T4 range (ng/dL)
Grade 1	4.0–10.0	Normal (0.9–1.7)
Grade 2	> 10.0	Normal (0.9–1.7)

Based on information from references 2 and 10.

The complex interplay of factors that influence thyroid hormone regulation makes the distinction between subclinical hypothyroidism and overt hypothyroid disease arbitrary.

IS THE UPPER LIMIT OF NORMAL FOR TSH TOO HIGH?

The true upper limit of normal of TSH to diagnose subclinical hypothyroidism is still debated.[14]

Currently, the normal reference range for TSH is extrapolated from population-based data, calculated from Gaussian distribution with 95% confidence intervals of studies of people who do not have thyroid disease, thyroid peroxidase antibodies, or thyroglobulin antibodies.[23] In most studies, the lower limit of TSH (the 2.5th percentile) was between 0.2 and 0.4 mIU/L, but the upper limit (the 97.5th percentile) varied between 2.4 and 4.2 mIU/L.[24]

Why was this range so wide? Many people in the studies actually had undiagnosed autoimmune thyroid disease (Hashimoto thyroiditis) or other factors that affect TSH, such as medications, nonthyroidal illness, pregnancy, subacute thyroiditis in the recovery phase, heterophilic antibodies, thyroid hormone resistance, TSH-receptor mutations, bio-inactive TSH, and TSH-producing pituitary tumors, or had their blood drawn at a high point in their circadian rhythm.[25] This renders the TSH distribution non-Gaussian, with a tail at the upper end.[26] If we take out these confounding factors, and a normal Gaussian distribution with a bell-shaped curve is achieved, the normal reference range becomes 0.4 to 2.5 mIU/L.[27]

In view of these studies, some have proposed lowering the upper limit of normal from 4.5 to 2.5 mIU/L.[24,27] However, Surks et al[28] argue against changing the upper limit, estimating that if we lower the upper limit of normal for TSH to 3.0 mIU/L to screen elderly patients with vague symptoms, it will label 22 to 28 million

TABLE 3
Factors that can affect serum thyroid-stimulating hormone (TSH) levels

Factor	Explanation
Time of day	TSH levels naturally fluctuate throughout the day, peaking in the early morning hours
Season of year	TSH levels may be slightly higher in winter than in summer, potentially due to changes in sunlight exposure or other environmental factors
Stress	Can temporarily suppress TSH production
Illness	Infections or autoimmune diseases can disrupt the hypothalamic-pituitary-thyroid axis, leading to changes in TSH levels, depending on the severity or duration of the illness
Medications	Some medications, particularly those used to treat thyroid disorders or other conditions, can influence TSH levels
Interindividual variation	There can be significant individual differences in TSH patterns, even among healthy individuals; genetic factors and personal characteristics may play a role
Age	TSH levels tend to increase with age, particularly in older adults
Sex	Some studies suggest that there may be sex-specific differences in TSH regulation, so that women tend to have higher TSH levels than men[14]
Autoimmunity	Autoimmune thyroid diseases such as Hashimoto thyroiditis can lead to elevated TSH levels, particularly in the early stages of the disease

Based on information from references 14–21.

more Americans as having subclinical hypothyroidism without evidence-based therapeutic benefit from this diagnosis. Instead, they suggest measuring the TSH level every 1 to 2 years in patients whose TSH levels are between 2.5 and 4.5 mIU/L.

WHY DOES TSH RISE WITH AGE?

Why TSH increases with age is not known.[29] In NHANES III,[12] TSH levels increased with age, and, interestingly, so did the prevalence of thyroid peroxidase antibodies and thyroglobulin antibodies. Some 14% of people older than 85 years had TSH levels higher than 4.5 mIU/L.

Hashimoto thyroiditis is the most common condition associated with subclinical hypothyroidism in the elderly, and in almost 90% of cases is characterized by antibodies against thyroid peroxidase and thyroglobulin.[11] Patients who had these antibodies progressed to having overt hypothyroidism at the rate of 4.3% per year, compared with only 2.6% in those without these antibodies.[30]

Once these antibodies are present, however, changes in their levels do not add more information while monitoring subclinical hypothyroidism, due to parallel fluctuation of TSH and thyroid peroxidase antibody.[31] These antibodies are not harmful to the thyroid glands; however, the volume of thyroid glands generally shrinks after 50 years of age, and pathology studies have found lymphocytic infiltration of the gland and fibrosis.[31] Thus, aging-associated thyroid cellular damage from cellular and humoral immune mechanisms with possible T lymphocytes was suspected.[11,32] Changes in iodine absorption and organification have been observed in elderly patients.[33] In addition, the normal nocturnal surge in TSH (possibly related to maintenance and repair mechanisms) is partially or completely lost. Thus, nighttime TSH levels are lower but 24-hour TSH levels are higher, to keep the T4 level normal.[17] Corticosteroid inhibitory function is also compromised in the elderly and leads to decreased hypothalamic-pituitary-thyroid inhibitory function.[11]

While a direct correlation between aging and mild thyroid failure is debated, there is evidence to suggest that some aspects of aging may resemble the symptoms and physiologic changes associated with mild hypothyroidism.[11] Whether this is a protective mechanism in the elderly or rather represents a diseased hypothalamic-pituitary-thyroid axis is debated.[34] In a study in southern Italy, Corsonello et al[35] found that older people had lower T4 and T3 levels and higher TSH levels—and so did the children and nieces and nephews of centenarians, suggesting that these changes might be associated with longevity.

Also, elderly patients have less circadian variation in TSH and a weaker response to thyrotropin-releasing hormone compared with the young, changes that are believed to conserve energy, particularly in those with reduced physical activity.[11,18]

IS SUBCLINICAL HYPOTHYROIDISM HARMFUL? IS TREATMENT BENEFICIAL?

Findings have been inconsistent regarding the potential harms of untreated subclinical hypothyroidism, and evidence that treatment is beneficial is lacking.

Cardiovascular disease

Thyroid hormones play a crucial role in regulating various bodily functions, glucose metabolism, protein synthesis, and cardiovascular function. However, the impact of thyroid hormones on the cardiovascular system, particularly in older adults with subclinical hypothyroidism, is inconsistent.[11]

In the Rotterdam Study,[36] TSH levels higher than 4.0 mIU/L with normal free T4 were associated with higher risks of myocardial infarction (odds ratio 2.3) and aortic calcification (odds ratio 1.7). When antithyroid antibodies were present, patients with subclinical hypothyroidism had greater progression to more severe atherosclerosis than euthyroid individuals.

Japanese men, average age 58.5 years, with TSH higher than 5.0 mIU/L and normal free T4 had a high risk of ischemic heart disease (odds ratio 4.0).[37] In Taiwanese people age 20 and older with subclinical hypothyroidism followed for 10 years, the all-cause mortality rate was 30% higher, and the rate of death due to cardiovascular disease was 68% higher than in euthyroid people.[38]

In contrast, a study that analyzed data from the Cardiovascular Health Study[13] found no links between subclinical hypothyroidism and adverse cardiovascular, cerebrovascular, or mortality outcomes. However, the range of TSH values was wide: 4.5 to 20.0 mIU/L.

A meta-analysis[39] found significantly greater risks for coronary heart disease morbidity and mortality in those with TSH levels 10 mIU/L and higher, and the risks increased significantly in those age 65 to 79 years, but not at age 80 or above, compared with euthyroid participants. In other meta-analyses that used data from the Thyroid Studies Collaboration cohort,[40–42] there was no association between subclinical hypothyroidism (with TSH levels in the range of 4.5–19.9 mIU/L) and stroke, atrial fibrillation, or heart failure.[19] Overall, the mortality rate was not higher than in euthyroid patients. However, the subgroup with TSH levels 10 mIU/L or higher had higher risks of heart failure, coronary heart disease events, and death from coronary heart disease than the euthyroid group. In addition, the risks of death from stroke and coronary heart disease were higher in those with TSH levels of 7.0 to 9.9 mIU/L.[39,40]

In a post hoc analysis of the Prospective Study of Pravastatin in the Elderly at Risk,[44] patients with subclinical hypothyroidism (age range 70–82 years) had significantly higher rates of heart failure and death, but only those with TSH levels higher than 10 mIU/L.

Razvi et al[45] performed a meta-analysis and found no difference in ischemic heart disease morbidity or mortality in patients age 65 or older with subclinical hypothyroidism, but did find increased mortality in patients younger than 65 years.

Cognitive dysfunction and depression

Thyroid hormones are essential for brain development; however, whether subclinical hypothyroidism affects cognition in elderly patients is questioned, and studies of this matter are inconclusive.[11]

Pasqualetti et al[46] conducted a meta-analysis of prospective and cross-sectional studies and found that subclinical hypothyroidism was associated with cognitive impairment in patients younger than 75, but not older. However, in the 2015 US Preventive Services Task Force study, Rugge et al[1] reviewed trials of treatment vs placebo for subclinical hypothyroidism (TSH 4.5–10 mIU/L or ≥ 10 mIU/L) and found no effects on cognitive skills or performance, speed or capacity of language processing, or psychomotor tests of executive functions. They rated the overall quality of evidence as "poor."

Dyslipidemia

Rugge et al[1] found only small changes in the average total cholesterol and low-density lipoprotein cholesterol levels with treatment, and no significant differences in high-density lipoprotein cholesterol levels or triglyceride levels between the treated and untreated groups.

Blood pressure

Rugge et al[1] found no evidence that treating subclinical hypothyroidism affected blood pressure in patients with TSH levels higher than 3.6 mIU/L.

Mortality

Some studies[13] found no significant association between subclinical hypothyroidism and mortality.

Quality of life and symptoms

The only large study that delved into hypothyroid symptoms such as dry skin, poor memory, cognitive slowing, muscle weakness, cold feelings, voice changes, constipation, and puffy eyes was the cross-sectional Colorado Thyroid Disease Prevalence Study.[47] Interestingly, 25% of individuals with overt hypothyroidism, 20% of those with subclinical hypothyroidism, and 17% of euthyroid individuals reported 4 or more symptoms commonly associated with hypothyroidism.

The Thyroid Hormone Replacement for Untreated Older Adults With Subclinical Hypothyroidism (TRUST) trial[4] included 737 adults 65 or older with TSH levels ranging from 4.6 to 19.99 mIU/L and normal free T4 levels, who were given levothyroxine (median dose 50 µg) or placebo. At 12 months, in the treated group, TSH levels had declined from 6.40 mIU/L to 3.63 mIU/L, but there was no clinical difference in the mean changes of hypothyroid symptoms score or in the tiredness score. These findings raise the question of whether subclinical hypothyroidism is a true disease or just a biochemical cutoff.

Kidney function

In theory, thyroid deficiency could affect kidney function by lowering cardiac output, although evidence does not support an association between subclinical hypothyroidism and kidney dysfunction.[48] However, patients on hemodialysis who had subclinical hypothyroidism had a higher mortality rate.[49]

Neuromuscular effects

Although there have been suggestions that neuromuscular symptoms are common in patients with subclinical hypothyroidism, more definitive answers are needed for those with TSH 10 mIU/L or below.[50] In several studies in elderly patients, there was no association between subclinical hypothyroidism and low bone mineral density, fracture risk, or frailty compared with euthyroid patients (reviewed by Biondi et al[19]).

HARMS OF OVERTREATMENT

Many patients with hypothyroidism are being overtreated. Biondi and Cooper[26] estimate that the overtreatment rate of subclinical hypothyroidism exceeds 20%. This overtreatment can lead to low TSH levels, potentially causing thyrotoxicosis in elderly patients. In 2 studies, 22% to 23% of patients on levothyroxine replacement had suppressed TSH levels.[47,51] At the Massachusetts General Hospital Thyroid Clinic, 14% of patients on levothyroxine therapy had suppressed TSH levels.[52]

Subclinical or overt thyrotoxicosis can lead to atrial fibrillation, cardiovascular events, reduced bone density, fractures, and increased mortality. A study in Denmark[53] followed a cohort of patients with overt and subclinical hypothyroidism every 6 months for a median of 7.2 years and found that the mortality rates of those who were overtreated with levothyroxine so that their TSH levels were lower than 0.3 mIU/L increased with duration of overtreatment.

GUIDELINES AND RECOMMENDATIONS

Several medical organizations have published guidelines for diagnosing and managing subclinical hypothyroidism. These differ somewhat, as medical research evolves and there is as of yet no universal consensus.

The European Thyroid Association, in its 2013 guideline,[10] recommends classifying subclinical hypothyroidism as mild or severe according to TSH level; if mild, it suggests no treatment but repeating this measurement 2 to 3 months later, along with thyroperoxidase antibodies. If the patient is younger (< 65–70) and has TSH higher than 10 mIU/L, treatment should be started. If a patient in this younger group has TSH lower than 10 mIU/L and normal free T4 but has symptoms, a trial of thyroxine can be considered. If the TSH level is normal after 3 to 4 months of thyroid replacement therapy, then symptoms should be reevaluated and therapy should be stopped if no symptomatic change is observed.

In older people, the European Thyroid Association recommends using age-specific local reference ranges for TSH to diagnose subclinical hypothyroidism (eg, TSH 4–7 mIU/L for those older than 80 years).[10] In patients older than 80 to 85 years with TSH 10 mIU/L or less, a wait-and-see strategy should be prioritized before starting replacement therapy, as deleterious effects of subclinical hypothyroidism on cardiovascular risk vanish in this group. If treatment is to be started in older patients (> 65–70 years), the target TSH range should be the lower half of the reference range, or 0.4 to 2.5 mIU/L. For patients without cardiac disease, a weight-based dose of 1.5 µg/kg/day should be used. In patients with preexisting cardiac disease, they say to start levothyroxine treatment low at 25 to 50 µg/day and increase it every 2 to 3 weeks to slowly bring TSH down to target.

In patients with persistent subclinical hypothyroidism, thyroid function tests should be checked every 6 months for the first 2 years, and then annually.

The American Thyroid Association and American Association of Clinical Endocrinology 2012 guideline[2] and their 2014 update[3] echo the European classification of mild vs severe subclinical hypothyroidism. In severe subclinical hypothyroidism, thyroxine treatment is generally supported, similar to the European recommendation. However, the American guideline is less specific regarding mild subclinical hypothyroidism. It recommends considering individual factors such as symptoms, thyroid peroxidase antibody status, and evidence of cardiovascular disease, especially in patients younger than 65 years.

The 2014 American Thyroid Association update[3] recommends starting low and titrating slowly in elderly

TABLE 4
Guidelines and recommendations on managing subclinical hypothyroidism

Organization	Mild subclinical hypothyroidism (TSH 4.0–10.0 mIU/L)	Severe subclinical hypothyroidism (TSH > 10.0 mIU/L)	Key comments
US Preventive Services Task Force (2015)[1]	Does not recommend routine screening or treatment	Recommends treatment	Insufficient evidence of benefit of treatment in patients without symptoms
European Thyroid Association (2013)[10]	Watchful waiting, unless symptomatic Consider treatment in younger individuals with persistent symptoms	Recommends treatment	Emphasizes a cautious approach, especially in older adults
American Association of Clinical Endocrinology and American Thyroid Association (2012)[2]	Does not recommend routine screening or treatment in patients without symptoms Consider treatment in select cases based on individual factors	Recommends treatment	Highlights individualizing treatment decisions and considering factors such as age, comorbidities, and symptom burden
American Thyroid Association (2014 update)[3]	Similar to 2012 guidelines, emphasizing individualized approach	Recommends treatment, particularly in younger individuals and those with specific risk factors	Reinforces the importance of considering individual factors and the potential benefits of treatment in certain cases
American College of Physicians (2019)[55]	Does not recommend routine screening or treatment unless symptoms are present	Recommends treatment	Emphasizes individualizing treatment based on patient factors
American Academy of Family Physicians (2021)[54]	Does not recommend routine screening or treatment unless symptoms are present	Recommends treatment	Highlights the lack of evidence for routine screening and treatment in patients without symptoms

TSH = thyroid-stimulating hormone

patients with hypothyroidism, and recommends raising the TSH target range to 4 to 6 mIU/L in persons 70 to 80 years old. It also cautions against iatrogenic thyrotoxicosis from overtreatment with levothyroxine, especially avoiding TSH levels lower than 0.1 mIU/L in older and postmenopausal women to avoid cardiac and bone deleterious effects.

Other organizations[22,54–56] have also issued recommendations regarding hypothyroidism diagnosis and treatment. Although these recommendations are not specific to subclinical hypothyroidism in the elderly, they generally concur with those above (**Table 4**).[1–3,10,54,55]

MANAGEMENT CHALLENGES

There are no uniform national guidelines on screening elderly patients with blood TSH levels for thyroid disease.

Although the association between increasing TSH and aging is well described,[2,10,47] the practice of using age-adjusted TSH reference ranges to diagnose elderly patients with thyroid diseases is not currently routine.[57] As a result, the current TSH normal range (0.4–4.5 mIU/L) is inappropriately used to diagnose subclinical hypothyroidism in patients older than 65 years, and this overestimates the prevalence of subclinical hypothyroidism and also leads to overtreatment.

Moreover, Danese et al[58] estimated the cost of routine screening in women older than 35 years every 5 years at approximately $9,200 per quality-adjusted year of life (this was in 1996, and the cost would be higher now), raising concerns about the feasibility and potential drawbacks of universal screening.

The concept of using a TSH cutoff value can also be deceiving. The test is based on a sample of healthy volunteers without thyroid disease or thyroid antibodies,

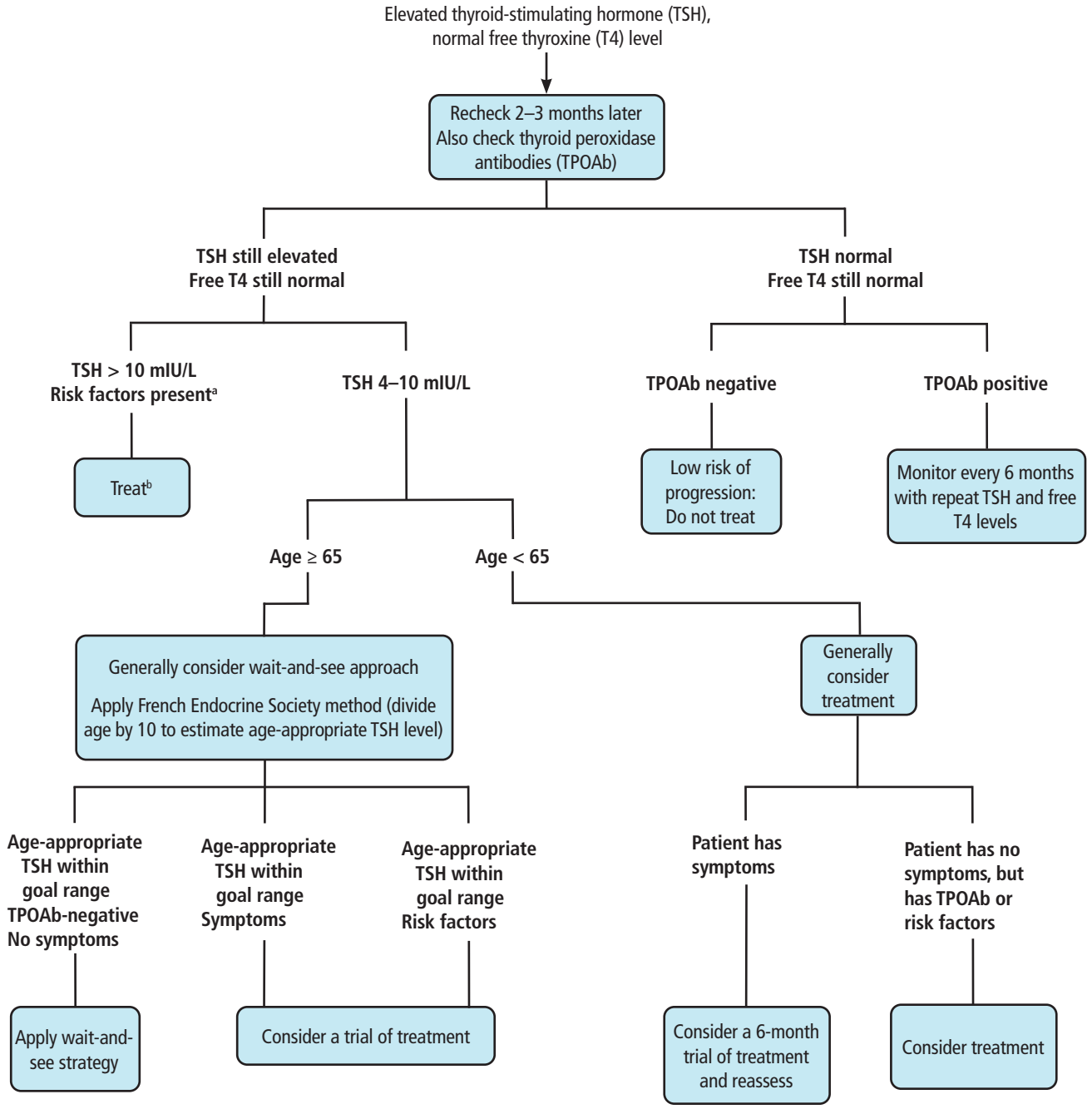

Figure 1. Flow chart for clinical decision-making in subclinical hypothyroidism.

[a]Risk factors: TPOAb-positive, goiter, atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases.
[b]Oral levothyroxine daily is the treatment of choice. For patients with cardiac disease, 1.5 µg/kg/day should be used. For elderly patients with cardiac disease, a dose of 25–50 µg/day is recommended. Increase dose by 12.5 to 25 µg/day every 2 to 3 weeks. Target TSH range is 0.4 to 2.5 mIU/L.

representative of a larger population and calculated with statistical methodology. However, many factors can affect this arbitrary reference range (**Table 3**).[17,59] For example, studies in urban populations over age 55 without thyroid peroxidase antibodies or other factors show higher TSH levels in White and Mexican American individuals than in Black individuals.[12,21] Scobbo et al[60] demonstrated that TSH fluctuates throughout the day, being significantly higher before breakfast (7:30–9:00 AM) than after breakfast (10:30 AM–12:00 PM), with an average decline of 26.4%.

Another problem with the use of a TSH cutoff to define subclinical hypothyroidism is that TSH changes can be transient and reversible. In a large retrospective longitudinal study,[61] 57.9% of patients with subclinical hypothyroidism reverted to euthyroid TSH levels during a median follow-up of 36 months. Unfortunately, most of the studies dealing with risks and benefits associated with subclinical hypothyroidism included patients who had no repeat TSH assessments to confirm the persistence of TSH elevation.[21,29] This raises the question of inconsistency in the benefits and risks of treating subclinical hypothyroidism. On top of this, observational studies did not address TSH status while receiving treatment.[13] All of these uncertainties contribute to the debate about the clinical relevance of subclinical hypothyroidism, especially in grade 1 subclinical hypothyroidism, and in older patients.

In summary, factors such as the time of day, ethnicity, and inconsistent TSH levels complicate accurate subclinical hypothyroidism diagnosis. Varied study methodologies and a lack of longitudinal TSH data further obfuscate the issue. The absence of age-appropriate diagnostic guidelines and consensus makes establishing clear evidence-based benefits difficult.

PHYSICIAN DECISION-MAKING AND ALTERNATIVES

While some studies have linked untreated subclinical hypothyroidism to cardiovascular issues and heart failure, the US Preventive Services Task Force reviewed multiple studies and found no significant clinical benefit from treatment in grade 1 subclinical hypothyroidism.[1] The 2017 TRUST randomized clinical trial supported these findings.[4]

To personalize the diagnosis and treatment, the French Endocrine Society[56] proposed a novel approach in their 2019 consensus statement—using the formula patient age divided by 10 to establish the upper limit of normal for TSH in patients older than 60. This approach acknowledges the potential for natural changes in TSH levels with age. Consequently, for an 80-year-old, the upper limit for TSH would be 8 mIU/L, which differs from the standard cutoff used for younger populations.

Recently, Kuś et al[16] reported a novel approach to personalizing TSH intervals: using a polygenic score system based on 59 genetic variants to calculate TSH reference ranges. This predicted 9.2% to 11.1% of total variance in TSH concentrations, compared with 2.4% to 2.7% with free T4. This reflects the idea that different individuals have different set points in their hypothalamic-pituitary-thyroid axis, and thus can have higher TSH concentrations at the same free T4 levels.[59]

In older patients, Calsolaro et al[11] recommend treating severe subclinical hypothyroidism with thyroxine. However, in patients with mild subclinical hypothyroidism, starting levothyroxine can be considered on a case-by-case basis according to symptoms, frailty, cardiovascular risk factors, and personal preferences. If a patient needs treatment, they recommend following the professional guidelines. Alternatively, mild subclinical hypothyroidism can be monitored without therapy by repeating laboratory tests every 3 to 6 months to monitor progression of overt disease and treated if TSH rises to more than 10 mIU/L.[2,10,58]

We propose an approach that combines the professional society guidelines and the French Endocrine Society 2019 consensus statement[56] with an age-based TSH cutoff (**Figure 1**). When the decision becomes complicated, consultation with a team including an endocrinologist and geriatrician is recommended.

A PERSONALIZED APPROACH

Subclinical hypothyroidism is common in the elderly and is going to be more so in the coming decades. Its management requires a personalized approach that weights the potential benefits and risks, as current evidence does not show a clear difference in outcomes if mild subclinical hypothyroidism is treated or not. Age-adjusted TSH reference ranges, consideration of individual circumstances, and a wait-and-see approach for mild cases might be more suitable than a universal treatment strategy.

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EDITORIAL

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Subclinical hypothyroidism: What's in a name?

In primary hypothyroidism, there is a decline of thyroid hormone production by the thyroid, leading to compensatory up-regulation of thyrotropin (thyroid-stimulating hormone [TSH]) production by the pituitary in an effort to maintain thyroid hormone levels. Primary gland failure is frequently a gradual process, occurring over years, with a long preclinical phase during which regulatory feedback mechanisms are able to maintain homeostasis.

See related article, page 221

With the advent of sensitive assays to measure TSH, the diagnosis of hypothyroidism moved from the detection of only severe cases based on the metabolic consequences of hypothyroidism, to simple blood tests that can detect altered regulatory feedback in the hypothalamic-pituitary-thyroid (HPT) axis, which can represent the early stages of gland failure. In more advanced cases, TSH is elevated and thyroxine (T4) levels are low, and primary hypothyroidism may be comfortably diagnosed. The concept of *subclinical hypothyroidism* was developed for those with elevated TSH and a compensated free T4 level within the reference range, opening the debate about whether to treat these patients, and at what threshold of TSH elevation, as discussed in detail by Xu et al[1] in this issue of the *Journal*.

Isolated elevated serum TSH in older adults

But there is an earlier question that is especially relevant in older adults, which is whether all individuals with an isolated elevated serum TSH level and reference-range T4 level should be grouped together using a single unified name. By definition, this group comprises 2.5% of the reference population, but a study of data from the third National Health and Nutrition Examination Survey found that the rates are much higher for some subgroups, with about 10% of 80-year-olds otherwise thought to be without thyroid disease meeting the standard definition of subclinical hypothyroidism.[2] Thus, before we debate whether to treat subclinical hypothyroidism, we need to know whether the laboratory findings actually uniquely signify emerging primary thyroid disease in this subpopulation—or is there some other explanation that we are missing? That is, we need to know whether all older adults with an elevated TSH actually have subclinical hypothyroidism, or whether the name is misleading us.

Several different groups in the past 20 years have made interesting observations about the dynamics of and associations with isolated elevated serum TSH levels in older adults. A provocative early study from the Netherlands found that 85-year-olds with higher TSH levels had better survival than those with normal or low levels,[3] although more heterogenous studies have not been able to replicate the findings.

A second important observation is that elevations in serum TSH levels are frequently transient, especially when the elevation is less than 10 mIU/L and antithyroid antibodies are negative. For example, in a cohort study, 35% of participants with an initial diagnosis of "subclinical hypothyroidism" had normal TSH levels at follow-up 2 years later, and of these, 48% had normal levels at the 4-year follow-up.[4] Similarly, a large, multicenter randomized trial of treatment for subclinical hypothyroidism in older adults that required 2 elevated TSH values 3 months apart to enroll failed to reach its recruitment targets and power for cardiac end points because of high rates of reversion to reference-range TSH levels on repeat testing.[5]

Finally, especially for TSH less than 10 mIU/L, it is not clear that not treating results in harm or that treating leads to benefits, while overtreatment is associated with risks, as highlighted in Xu et al.[1] For example, a randomized controlled trial of levothyroxine treatment in more than 700 patients (Thyroid Hormone

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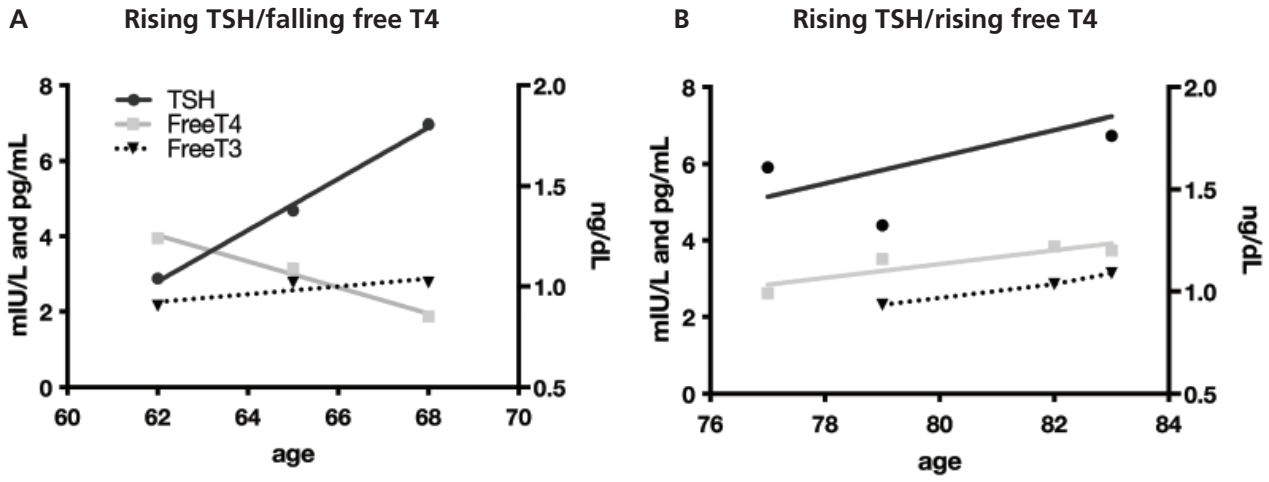

Figure 1. Varied patterns of hypothalamic-pituitary-thyroid axis hormone changes during aging in the Baltimore Longitudinal Study of Aging, with (A) a rising thyroid-stimulating hormone (TSH) accompanied by a falling free thyroxine (T4) level and (B) a rising TSH accompanied by a rising free T4 level.

T3 = triiodothyronine

Reprinted from Mammen JS, McGready J, Ladenson PW, Simonsick EM. Unstable thyroid function in older adults is caused by alterations in both thyroid and pituitary physiology and is associated with increased mortality. Thyroid 2017; 27(11):1370–1377. doi:10.1089/thy.2017.0211, with permission from Mary Ann Liebert, Inc.

Replacement for Untreated Older Adults With Subclinical Hypothyroidism [TRUST]) did not find any effects of therapy on symptoms or cognitive function.[5]

Heterogeneity of aging-related HPT axis changes

To examine the heterogeneity of HPT axis changes in aging, we analyzed the individual trajectories for TSH and thyroid hormone together for 640 participants in the Baltimore Longitudinal Study of Aging with 3 or more measurements over an average 7 years of follow-up.[6] We found that individuals with a similarly elevated TSH at their most recent study visit can have very different hormonal feedback histories (**Figure 1**).[6] A more rapidly rising TSH has been accompanied over time by a falling free T4 (**Figure 1, panel A**), a pattern that would be consistent with developing hypothyroidism and a current diagnosis of subclinical hypothyroidism. However, the more gently rising TSH is accompanied by a slightly rising free T4 (**Figure 1, panel B**) and suggests a distinctly different phenotype.

Many alternative mechanisms could underlie the heterogeneity in the biology of serum TSH elevations in older adults. Interesting hypotheses include decreased biological activity of TSH itself due to altered glycosylation; there could be an acquired central thyroid hormone resistance as a result, perhaps, of changes in pituitary expression of thyroid hormone transporters or response to thyroid hormone receptor activation; or there could be decreased peripheral deiodinase activity in the setting of chronic inflammation and stress, similar to the changes that occur during acute nonthyroidal illness.

Most important, the presence of this heterogeneity reminds us that the HPT axis does not operate in isolation. Central regulation is located not in the pituitary but in the hypothalamus, where things like energy balance and nutrition, inflammation, and circadian rhythm are integrated to ensure that thyroid hormones, which are catabolic, are at levels appropriate for the homeostatic needs of the whole person. If individuals with elevated TSH due to an alternative mechanism are treated with thyroid hormone, it is plausible that a decrease in serum TSH levels to "euthyroid" ranges would represent an inappropriate overriding of these potentially stress-related compensations.

Unfortunately, because we do not have a robust means of clinically phenotyping this heterogeneity, the goal of a personalized medicine approach that tailors use of thyroid hormone therapy in older adults based on their individual diagnosis remains unfulfilled for now. However, this uncertainty is yet another reason for caution when considering therapy, in addition to those highlighted in Xu et al[1]: the relative lack of harm associated with isolated serum TSH elevations less than

10 mIU/L,[7] lack of demonstrated benefit in those who are treated,[5] and possible harm associated with overtreatment.[8] Among those thought to have "subclinical hypothyroidism" are individuals who do not truly have that condition. These individuals might be at greater risk from treatment than those with the condition (in whom evidence suggests treatment is unnecessary) if the treatment overrides a change in the HPT axis function that is, in fact, adaptive or working to compensate for aging-related changes in function. Clinicians should remain thoughtful about the variability in aging biology and not be blinded by a name.

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DISCLOSURES

Dr. Mammen has disclosed serving as a research principal investigator for Interpace Diagnostics.

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CME MOC

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Nociplastic pain: A practical guide to chronic pain management in the primary care setting

ABSTRACT

Management of chronic pain is one of the most challenging medical issues in primary care. Effective pain management requires an understanding of nociplastic pain, a condition characterized by amplification of pain transmission and pain perception. Unlike nociceptive and neuropathic pain, nociplastic pain does not involve visible tissue injury or damage, which makes it difficult to understand and manage. This review discusses practical ways for primary care clinicians to identify and manage nociplastic pain at the point of care.

KEY POINTS

The most common barriers to effective pain management should be identified and addressed in the primary care setting, along with mitigation strategies, to achieve better pain control.

An alliance between the patient and primary care clinician is important because it increases treatment receptiveness, motivation, and adherence.

Nonpharmacologic treatment options are preferred because they have fewer side effects, greater availability, and sustained positive effects.

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Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[1] Pain that persists beyond the expected healing period of 3 months is defined as *chronic pain*.[2] Chronic pain can have a profound negative impact on a patient's emotional and social well-being[2] and exacts high societal costs as well. In the United States, the estimated societal cost of chronic pain is $560 to $635 billion per year, much higher than the economic impact of heart disease, diabetes mellitus, human immunodeficiency virus infection, Alzheimer disease, and even cancer,[3] and chronic pain accounts for 53% of indirect costs.[4] Moreover, 2.5% to 4.5% of gross domestic product in the United States is spent on chronic pain.[3]

More than half of patients receive care for chronic pain in the primary care setting.[5] Given that chronic pain is highly prevalent—more than the combined incidences of diabetes, heart disease, and cancer in the United States—a large percentage of primary care clinicians will manage chronic pain in their practices.[3] Thus, it is imperative that they understand how to manage pain safely and effectively.

PAIN CATEGORIZATION

Pain can be characterized into 3 mechanistic phenotypes.[6]

Nociceptive pain arises from tissue damage, injury, or degeneration caused by trauma, osteoarthritis, and joint inflammation (eg,

TABLE 1
Mechanistic types of pain

Pain type	Defining characteristics	Examples	Treatment
Nociceptive	Pain due to tissue injury, inflammation, damage, or degeneration	Osteoarthritis, rheumatoid arthritis, fracture, burns	Topical analgesics, nonsteroidal anti-inflammatory drugs, acetaminophen, opioids, steroids
Neuropathic	Pain due to nerve injury or damage	Radiculopathy, diabetic neuropathy, chemotherapy-induced neuropathy	Topical or local therapy; systemic neuropathic medications such as gabapentin, pregabalin, and tricyclic antidepressants
Nociplastic	Pain arising from a sensitized nervous system (amplified processing of pain signals, decreased inhibition of pain, or both)	Fibromyalgia, chronic back pain, chronic temporomandibular pain disorders	Multimodal management approach

Based on information from reference 6.

rheumatoid arthritis). It is localized to the area of the damage, injury, or inflammation, and can respond to topical or systemic therapies, including nonsteroidal anti-inflammatory drugs, opioids, and corticosteroids.[7]

Neuropathic pain is a result of nerve injury or damage, such as traumatic nerve injury, diabetic neuropathy, sciatica or radiculopathy from mechanical nerve compression, or medication- or chemotherapy-induced neuropathy. The pain can be localized to the area of nerve injury or damage, or it can follow a dermatomal distribution, causing characteristic features of sharp, shooting, burning pain along with tingling and numbness.[7] It can respond to local therapy and systemic neuropathic medications like gabapentin, pregabalin, and tricyclic antidepressants.

Nociplastic pain, the third and less well-known category of pain, arises from a sensitized nervous system, a condition known as *central sensitization syndrome*.[7] Nociplastic pain involves dysfunction in the central nervous system pathways, including amplified pain-signal processing, decreased signaling of the descending pain inhibitory pathway, or both.[8] In contrast to nociceptive pain, there is no demonstrable tissue damage. Nociplastic pain is usually associated with more subjective symptoms rather than objective findings, which makes understanding and managing it a formidable task.

Table 1 summarizes the 3 mechanistic phenotypes of chronic pain.[6]

MECHANISMS OF NOCIPLASTIC PAIN

The basic mechanism of nociplastic pain is a heightened pain sensor with amplification of pain transmission and pain perception.[8] Specifically, nociplastic pain can be explained by **top-down pain amplification** (via alteration in the descending pain-modulatory pathway, causing diminished efficacy of the pain-inhibitory pathway and increased activity of the pain-facilitatory pathway) and **bottom-up pain facilitation** (the ascending pathways in the central nervous system become overstimulated by peripheral inputs), leading to hyperalgesia and allodynia (**Figure 1**).[7]

The heightened pain sensitivity and associated features in nociplastic pain conditions (eg, fatigue, poor sleep, brain fog) are driven by central nervous system and peripheral mechanisms.[9]

Supraspinal mechanisms

- Hyperactivity and connectivity in and between brain regions involved in pain, but decreased activity of regions involved in pain inhibition
- Altered size and shape of brain regions involved in pain processing
- Increased levels of neurotransmitters associated with pain signaling (substance P, glutamate) in cerebrospinal fluid and decreased gamma-aminobutyric acid neurotransmission
- Glial cell activation

Spinal mechanisms

- Clustering and convergence of signals from different pain loci
- Spinal cord reorganization
- Increased spinal reflex transmission and diminished spinal inhibition
- Temporal summation (repeated stimulus evokes increased pain sensation)
- Glial cell activation

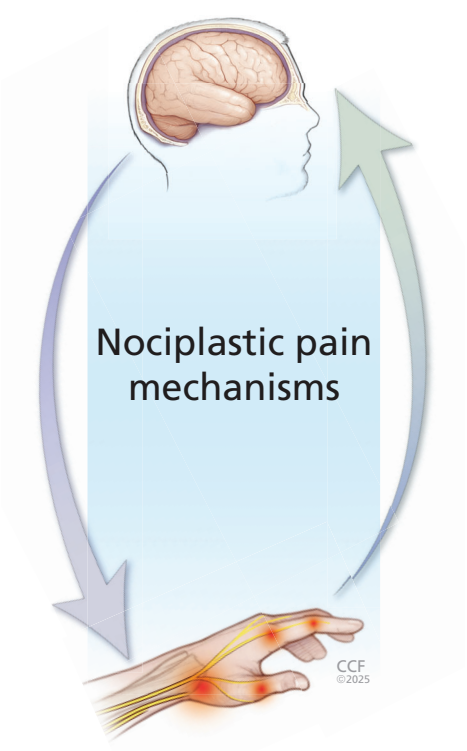

Figure 1. The mechanisms underlying nociplastic pain can be grouped into 2 broad categories: top-down (dysregulation in descending pathways involved primarily in pain inhibition) and bottom-up (dysregulation in ascending pathways primarily involved in pain facilitation).

Based on information from reference 7.

Peripheral mechanisms

- Minor local muscle pathology (eg, latent and active trigger points)
- Peripheral sensitization (eg, expansion of receptive fields, increased concentrations of cytokines and chemokines)
- Hyperalgesia, dysesthesia, and allodynia
- Localized or diffuse tenderness, or both

This pain-enhancement phenomenon may help explain how nociceptive and neuropathic pain lead to the evolution of nociplastic pain. For example, a patient with acute lower back pain and lumbar disc herniation often has nociceptive pain from the degenerated disc and neuropathic pain (radiculopathy) from nerve compression. Over time, the patient may also develop nociplastic pain. This highlights the importance of adequate and timely control of nociceptive and neuropathic pain in reducing the risk of developing coexisting chronic nociplastic pain.[10]

Chronic lower back pain is also an example of a condition in which nociceptive, neuropathic, and nociplastic pain can coexist, even though the 3 categories of pain remain distinct. Such conditions lend credence to the concept of a pain continuum,[9] as shown in **Figure 2.**[7] Given this pain continuum, effective management should address all 3 types of pain, as managing 1 type without addressing the others can result in inadequate pain control.

CHALLENGES AND MITIGATION STRATEGIES

Chronic pain is often frustrating to both patients and primary care clinicians because identifying nociplastic pain can be difficult and take time, and effective treatment modalities are limited. Further, when a patient visits their primary care clinician for chronic pain, they may worry about how their complaint will be perceived. Because nociplastic pain has no visible tissue injury or damage, patients may fear it will be mistakenly labeled by primary care clinicians as "made-up pain," "all in your head," "mental illness," or "drug-seeking behavior." This fear can prevent them from talking freely about their pain,[11] and can make them apprehensive about following the clinician's recommendations. Moreover, primary care clinicians often lack the knowledge and training needed to identify and manage nociplastic pain,

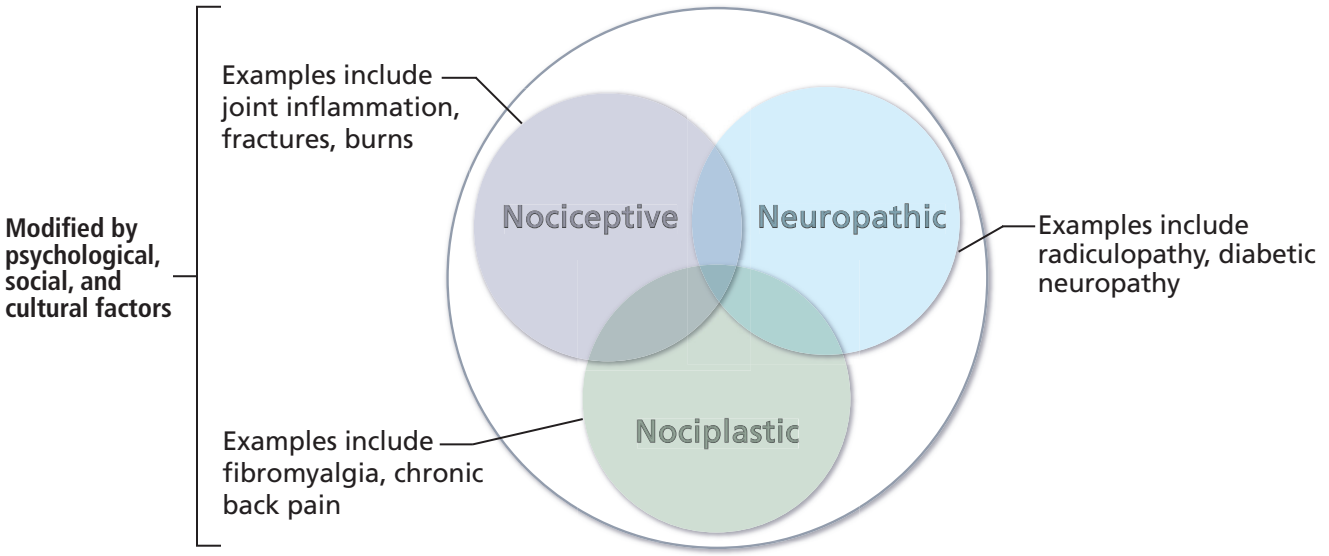

Figure 2. The pain continuum. There are 3 main categories of pain—nociceptive, neuropathic, and nociplastic—and these 3 types of pain can coexist.

Based on information from reference 7.

a problem compounded by the nature of the primary care setting, where multiple medical issues must be addressed within a short period of time. It is important to identify and address these barriers with patients to achieve better pain control. **Table 2**[10–15] outlines the most common barriers to effective pain management in primary care along with strategies to mitigate them.

Patients with chronic pain can fear having conditions like autoimmune arthritis, multiple sclerosis, or even malignancy. This fear can fuel the patient's anxiety and contribute immensely to the pain-amplification process, making it imperative that primary care clinicians explore and resolve any of these concerns. Explaining the symptom differences between inflammatory arthritis and osteoarthritis or mechanical arthritis and nociplastic or fibromyalgia-like pain can help reduce anxiety.[7] **Table 3** provides simple explanations of the 3 pain types that patients can understand easily.[7]

HOW TO IDENTIFY NOCIPLASTIC PAIN

Conditions that typically cause nociplastic pain can be localized (**Table 4**)[9] or widespread (eg, fibromyalgia) and are known as *chronic overlapping pain conditions*.[7] These conditions often occur together. Widespread nociplastic pain is often accompanied by diffuse tenderness, disabling fatigue, cognitive symptoms, and nonrestorative sleep.[16]

Concurrent symptoms

Nociplastic pain commonly occurs in combination with certain symptoms (**Table 5**).[9] Central sensitization, generalized hypersensitivity, and associated autonomic dysfunction possibly contribute to these concurrent symptoms.[8] Some patients with nociplastic pain may also have postural orthostatic tachycardia syndrome due to the same mechanisms.[17]

Standardized scales

Several standardized scales can be used to estimate the probability that nociplastic pain is present. The 2 scales that are most feasible to implement in the primary care setting are the Central Sensitization Inventory and the Central Aspects of Pain questionnaire.

The **Central Sensitization Inventory** is a simple, validated questionnaire developed to help identify patients with central sensitization, which would indicate they are also experiencing central sensitivity syndrome.[18] It has 2 sections. Part A measures 25 health-related symptoms common to central sensitivity syndrome, such as pain, hypersensitivity, mood, and energy, on a numeric scale; a score of 40 or higher out of 100 indicates central sensitivity syndrome. Part B lists previous diagnoses specific to central sensitivity syndrome. The more of these diagnoses a patient has, the greater the likelihood of central sensitization.[19] The questionnaire, including instructions, can be accessed at pridedallas.com/questionnaires/.

TABLE 2
Barriers and mitigation strategies for appropriate pain management

Barrier: *Previsit bias*
Mitigation: Eliminate any bias or negativity before the visit when the primary reason is "chronic pain" or "fibromyalgia" to improve clinician receptiveness and reduce frustration[13]
Avoid dismissive attitude toward the pain complaint[10,11]
Believe patient reports of the severity and adverse effects of pain
Barrier: *Difficulty connecting with patients and winning their confidence and trust*
Mitigation: Be empathetic and acknowledge that the pain is real; validating and legitimizing the pain can be emotional for patients and helps increase their trust and receptiveness[11]
Let patients narrate their symptoms and fully explain the impact of pain in their lives, which provides a crucial sense of being heard[10]
Debunk the myth that nociplastic pain is not a real condition and explain that the pain is not imagined or all in their head to make patients feel believed and heard[12,13]
Express to patients that we understand their pain and we will partner with them to help manage it as best we can
Share decision-making to reduce frustration toward clinicians and increase patient receptiveness, motivation, and adherence to therapeutic recommendations
Barrier: *Unrealistic or unreasonable expectations*
Mitigation: Patients may hope that a "magic pill" will fix the problem, and that can lead to frustration
Set realistic expectations upfront (eg, improve physical function), but be extremely empathetic[14]
Reassure patients that adequate pain control can be achieved, although the fix is not easy
Enable patients to take charge of their pain management, but provide assurance that they will always be supported
Barrier: *Overexpectation to completely eliminate the problem*
Mitigation: Focus on legitimizing and validating pain while also determining any acute causes of a pain flare
Accept that adequate pain management may not be curative, but even limited pain relief may enable patients to revive skills, renew social interactions, and improve quality of life
Modest gain in pain relief can significantly increase patient confidence in overcoming the pain and is a vital clinical accomplishment[11]
Focus on both the biological and psychosocial determinants of chronic pain (ie, mind–body dualism)[13]
Barrier: *Poor understanding of nociplastic pain and contributory factors*
Mitigation: Explain pain physiology to patients, which may improve health status (less worry about pain and long-term improvement in physical functioning, vitality, mental health) and increase endogenous pain inhibition in patients with fibromyalgia[15]
Barrier: *Appointment time constraints*
Mitigation: Schedule a separate appointment focused only on pain management; defer rest of care to another visit
Schedule a few extended appointments at first to allow time to really listen to patients
Barrier: *Diagnosis challenge and lack of knowledge and training*
Mitigation: Diagnosis is difficult due to inconsistent symptom recognition and diagnosis validity and lack of robust guidelines; even when guidelines are available, level of awareness may vary[11]
Learning about nociplastic pain and management principles is crucial
Barrier: *Referrals and resources*
Mitigation: Multidisciplinary approach can be helpful, but avoid unnecessary referrals that can lead to frustration
Create achievable short- and long-term pain management goals

The self-reported **Central Aspects of Pain** questionnaire consists of 8 items related to depression, anxiety, catastrophizing, cognition, sleep, and fatigue, and includes a body-pain manikin.[20] The questionnaire is a validated measure that assesses the centrality of chronic pain; it best assesses widespread pain in patients who mark 10 or more painful sites out of 26 on the body manikin. Studies have shown that a body manikin, or body map, can be the single most helpful tool to diagnose nociplastic pain.[21] The questionnaire, body manikin,

TABLE 3
Simplified ways to explain and compare different types of pain

Autoimmune inflammatory arthritis	Osteoarthritis or mechanical arthritis	Nociplastic pain or fibromyalgia
Autoimmune inflammation of the joints or tissue	Related to tissue injury or degeneration	Heightened pain sensitivity at the brain and spinal cord level
Presence of red, hot, swollen joints with palpable joint fluid and warmth	Can have transient morning pain and stiffness lasting less than 15 to 30 minutes	Pain is usually widespread with associated diffuse tenderness
Symptoms most pronounced in the morning and starts improving after 30 to 60 minutes of moving	Pain worsens with activity and joint use throughout the day	Related fatigue, poor sleep, brain fog, or irritable bowel symptoms
Rest aggravates pain and stiffness	Symptoms more prominent in the evenings, especially when joints were used more throughout the day	Worsens with poor sleep and stress
Responds to low-to-moderate dose of steroid; symptoms return after medication cessation	Rest makes the pain better except for transient pain and stiffness when getting up after a period of rest (ie, gelling phenomenon)	

Based on information from reference 7.

and scoring guide can be accessed at academic.oup.com/rheumatology/article-lookup/doi/10.1093/rheumatology/keae342#supplementary-data

Beighton criteria

The Beighton criteria should be used to check for evidence of joint hypermobility.[22] Hypermobility arthralgia is a specific type of nociceptive pain that is more common in younger patients. It is often described as pain in multiple joints after overuse, especially after playing sports. Physical therapy and using splints to help prevent joint hyperextension can make a significant difference in the patient's quality of life.

UTILITY OF AUTOIMMUNE LABORATORY TESTS FOR CHRONIC PAIN

Because pain is a prominent symptom of autoimmune connective tissue diseases, primary care clinicians often order laboratory tests such as antinuclear antibody, rheumatoid factor, and inflammatory markers in patients with chronic pain. Notably, these tests can be nonspecific. For example, up to 20% of the general population test positive for antinuclear antibodies, and a positive test by itself is not sufficient to diagnose systemic lupus erythematosus.[23] Moreover, inflammatory markers can be elevated in conditions like infection, malignancy, high body mass index, and untreated obstructive sleep apnea.[24] We strongly discourage ordering these tests in the absence of appropriate clinical manifestations (eg, persistently swollen joints, photosensitive rash, unexplained cytopenia or proteinuria, or pleural effusions) given the potential negative outcomes such as increased psychological distress and unnecessary healthcare spending.

NOCIPLASTIC PAIN MANAGEMENT

Effective pain management starts with following barrier mitigation strategies (**Table 2**), exhibiting empathy, and securing the patient's trust.[7] An alliance between the patient and primary care clinician is important because it increases treatment receptiveness, motivation, and adherence.

Nonpharmacologic treatment options should be the first line of therapy because they have fewer side effects, are widely available, and have sustained positive effects.[25]

Self-care and management

Social support. When a patient has chronic pain, it affects not only the patient but also the family. Sharing frustrations and anxiety with family and support groups can provide catharsis and increase motivation to learn pain-coping skills.[11] Learning how other patients successfully manage similar pain can be helpful and inspiring.

Healthy lifestyle. Adopting general healthy lifestyle measures like regular exercise, good nutrition, proper sleep hygiene, smoking cessation, and ergonomic modifications can have a positive impact on pain control.[9]

Good communication skills and awareness of sensitive topics. For example, a discussion about weight loss, when appropriate, should be done in a nonthreatening manner because some patients may find it offensive, which could act as a barrier to further care.

Mental health. Seeking help from a mental health professional can enable patients to learn adaptive pain-coping skills in challenging situations. The timing of a referral to a mental health professional depends

TABLE 4
Localized conditions that cause nociplastic pain

Chronic primary headache and orofacial pain
Chronic migraine
Chronic tension-type headache
Trigeminal autonomic cephalalgias
Chronic temporomandibular pain disorders without anatomic abnormality or explanation
Chronic burning mouth
Chronic primary orofacial pain

Chronic visceral pain syndrome
Chronic primary bladder pain syndrome or interstitial cystitis
Chronic pelvic pain syndrome
Irritable bowel syndrome
Chronic chest pain
Chronic abdominal pain

Chronic primary musculoskeletal pain
Primary cervical, thoracic, lower back, and limb pain; extent of pain and suffering is greater than expected based on the underlying pathology[9]
Complex regional pain syndrome

TABLE 5
Symptoms and factors indicative of nociplastic pain

Difficulty localizing pain
Chronic fatigue
Memory problems (ie, brain fog)
Anxiety or depression
Poor sleep quality
Irritable bowel symptoms
Chronic headache
Chronic pelvic pain
Hypersensitivity to nonpainful stimuli (light sensitivity, sound sensitivity, allodynia or hyperalgesia)
Report of more comorbid illnesses
Intolerance to multiple medications without true allergy
Frequent use of healthcare services

Based on information from reference 9.

on the patient's receptiveness and degree of trust toward the primary care clinician. The topic should be introduced cautiously because a blunt presentation could sever the established relationship with the patient.

Graded aerobic exercise

Short-term aerobic training. Training at the intensity recommended to increase cardiorespiratory fitness provides important benefits, including improved physical function and possible pain relief.[16] Getting to the aerobic stage of exercise (with heart-rate increase and sweating) can result in activation of pain-inhibitory and endogenous endorphin pathways and release of "feel good" hormones.[26] Exercise can reduce fatigue, improve depression and fitness, and positively affect neuroplasticity, leading to improvements in sleep, memory, and emotional and cognitive functioning.[16,27]

When patients with nociplastic pain start exercising, they tend to hurt more initially due to their heightened pain sensitivity. Therefore, preparing patients psychologically, reiterating the importance of a graded approach and stressing the need to start slowly, can improve adherence to exercise.[28] Patients should be reassured that maintaining a consistent aerobic exercise program will make them feel better over time, which can also help with long-term adherence.

Even if patients are not able to achieve an aerobic level of exercise, movement itself can be beneficial for pain control. For patients with available resources, aquatic aerobics or water therapy (preferably in warm water due to temperature sensitivity) can be particularly helpful for those with underlying arthritis and high body mass index because it can be less painful than land-based exercise.

See the Resources section below for recommended forms of exercise.

Psychoeducational therapy

Different forms of psychotherapy can have a positive impact on nociplastic pain.[9] The main goal with these therapies is to "turn down the symptom dial" of the body's pain sensor (like turning down a volume dial). Options include the following:

- Cognitive behavioral therapy
- Mindfulness and acceptance-based interventions
- Psychodynamic therapies
- Biofeedback
- Hypnotherapy.

Table 6[29–36] outlines the components and benefits of various psychoeducational therapies. The Resources section also lists links to online resources that patients can access.

Physical and alternative therapies

Other nonpharmacologic therapies like acupuncture, massage therapy, virtual reality, transcutaneous electrical nerve stimulation, heat therapy, and cryotherapy have been shown to have some role in managing chronic pain and are thought to work by modulating chronic pain signals through physiologic mechanisms.[32]

TABLE 6
Psychoeducational therapies for nociplastic pain

Type and components	Description
Cognitive behavioral therapy	A technique to cope with pain and convert unpleasant stimuli to pleasant stimuli
	Focuses on reducing pain and distress by modifying physical sensations, catastrophic thinking, and maladaptive behaviors[29]
Distraction	Involves engaging in thoughts or activities (eg, finding joy, relaxation techniques, diaphragmatic or belly breathing, social activities) that distract from pain
	One of the most used and highly endorsed strategies for controlling pain[30]
Activity pacing	A 2-part strategy that involves spending just enough time on an activity to get the most out of it without pushing so far that patients experience more pain; over time, patients may be able to do more
	1. Conserve energy for activities patients value (eg, playing with their kids or undertaking a pleasurable recreational activity)
	2. Set graduated activity quotas to help increase ability to do activities (tolerance) and reduce disability
Cognitive restructuring	Helps reframe negative thoughts into more positive adaptive thoughts
Other	Includes relaxation, guided imagery, and meditation that can be helpful with pain management
	Telehealth can be an excellent resource, particularly for patients with inadequate access to mental health professionals[31]
Mind–body therapy	
Mindfulness	A nonelaborative, nonjudgmental awareness of the present-moment experience[32]
	Involves breathing methods, guided imagery, and other techniques to relax the body and mind and to help reduce stress
	Uses cognitive reappraisal to help separate the sensation of pain from the alarm reaction, which reduces the pain experience[33]
	A recent study on veterans with chronic pain showed telehealth-based mindfulness intervention improved pain-related function and biopsychosocial outcomes compared with standard care[34]
Tai chi	A mind–body activity that combines meditation with slow, gentle, graceful movements, as well as deep breathing and relaxation, to move vital energy (or qi) throughout the body
	A complex multicomponent intervention that integrates physical, psychosocial, emotional, spiritual, and behavioral elements[35]
	Evidence shows clinically important improvements in symptoms, disability, and quality of life in patients with chronic widespread pain[36]
Yoga	Evidence supports a role in reducing nociplastic pain[32]
Psychodynamic therapy	An in-depth form of talk therapy that focuses on unconscious processes based on previous unresolved conflicts or dysfunctional relationships that can shape present behavior
	Goal is to create self-awareness and understand how the past influences present behavior and then rectify it
	Focuses more on the patient's relationship with the external world rather than the patient–therapist relationship
Hypnosis and hypnotherapy	Explores the subconscious mind and causes an altered state of consciousness to prevent normally perceived experiences, such as pain, from reaching the conscious mind

Sleep hygiene

Nonrestorative or poor-quality sleep is associated with fatigue and tiredness and can contribute to pain amplification. Nonrestorative sleep is a strong predictor of chronic widespread pain because sleep is necessary to repair the body and decrease neuronal activity.[7]

Evaluation and treatment of obstructive sleep apnea and insomnia (difficulty falling asleep, staying asleep, or both) is vital to mitigate the pain amplification and fatigue that results from poor-quality sleep.

Sleep hygiene techniques like yoga, blue-light avoidance, changes to the sleeping environment (eg, removing televisions, screen-time reduction), avoiding exercise close to bedtime, and limiting caffeine can help patients achieve restorative sleep. Sleep-specific cognitive behavioral therapy can help improve insomnia and thereby improve pain.

As a last resort, low-dose trazodone, doxepin, or cyclobenzaprine can be considered for coexisting sleep disturbances that can amplify pain.[37,38]

Pharmacotherapy

Different medications are used on- and off-label to treat nociplastic pain. It is important to note that these medications have shown only modest efficacy and are fraught with adverse side effects[39] and a low adherence rate.[40]

Traditional analgesic treatments such as muscle relaxants, nonsteroidal anti-inflammatory drugs, acetaminophen, and opioids are less effective for nociplastic pain than for nociceptive pain, and the use of opioid analgesics is strongly discouraged.[9,41]

Low-dose naltrexone, an opioid antagonist, has shown some benefit for chronic back pain and complex regional pain.[9] It is thought to work by activating more opioid receptors, leading to increased response to endogenous opiates. Low-dose naltrexone may also improve memory problems commonly seen in patients with fibromyalgia.[42]

Duloxetine, milnacipran, and pregabalin are the 3 US Food and Drug Administration–approved medications for the treatment of fibromyalgia.[43] Duloxetine had greater efficacy in treating pain and depression. Pregabalin was effective in reducing pain and improving sleep and quality of life.[44]

Tricyclic antidepressants such as amitriptyline,[43] nortriptyline,[45] and cyclobenzaprine as well as the alpha 2 delta ligand gabapentin[43] are frequently used off-label. Amitriptyline has the most evidence for improving pain, sleep, fatigue, and overall quality of life.[43]

A summary of pharmacologic approaches is outlined in **Table 7.**[14,46]

COORDINATED CARE

The management of nociplastic pain involves a multidisciplinary approach, including referrals to other specialties (eg, pain specialists). Although referral to pain management can be helpful, the general management principle is to use nonpharmacologic and intervention techniques as described above. Referrals to several different healthcare professionals and time-consuming appointments, especially if not coordinated (ie, each professional trying to manage the disease in their own way), can be exhausting to patients and may hinder improvement. In contrast, coordinated care managed by a primary care clinician can have a favorable outcome.[12]

FINAL THOUGHTS

Management of chronic pain, particularly of the nociplastic type, is challenging and, at times, may seem like fighting an invisible enemy. We must use all available resources, and that starts with securing buy-in from patients with nociplastic pain. If patients are not invested, all management strategies are set to fail from the start.

The vast array of treatment modalities can be overwhelming for primary care clinicians. In our opinion, the best approach is to select a few options that are accessible to and practical for patients because they will be more likely to adhere to them. An initial approach could be starting with simpler self-management recommendations like regular exercise and pleasant activity scheduling followed by activity pacing. In more severe cases, healthcare professional–directed talk therapy or prescription medications can be considered.

RESOURCES

Primary care clinician training

- Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians (acpjournals.org/doi/10.7326/M16-2367)
- American Geriatrics Society guideline for the pharmacological management of persistent pain in older persons (agsjournals.onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2009.02376.x)

Exercise regimens

- Fibromyalgia-friendly exercises (www.webmd.com/fibromyalgia/ss/slideshow-fibromyalgia-friendly-exercises)

TABLE 7
Pharmacotherapy options for nociplastic pain

Drug class and medication	Predominant symptoms and dose	Potential side effects
Selective serotonin-norepinephrine reuptake inhibitors	Pain and depression	
Duloxetine	Start at 30 mg in morning; can increase to 60 mg daily in a few weeks as tolerated[14]	Nausea, headache, diarrhea; do not stop suddenly—taper off gradually
Milnacipran	Start at 12.5 mg in the morning, increase by 12.5 mg every few weeks to 50–100 mg once or twice daily as tolerated[14]	As above
Tricyclic antidepressants	Pain, sleep, fatigue, and overall quality of life	
Amitriptyline	Start at 5–10 mg 1 to 3 hours before bedtime; increase by 5 mg no more frequently than every 2 weeks; use lowest dose possible (20–30 mg)[46]	Dry mouth, dry eyes, blurred vision, flushing, constipation, urinary retention, dizziness, drowsiness, cardiac arrythmia
Nortriptyline	Start at 10 mg at bedtime; up to 75 mg maximum[46]	Like amitriptyline but preferred due to fewer anticholinergic side effects
Alpha 2 delta ligands	Prominent sleep disturbance	
Pregabalin	Start at 25–50 mg at bedtime; increase by 25–50 mg every 2 to 4 weeks to 300–450 mg daily (in 1 or 2 divided doses) as tolerated[14]	Dizziness, drowsiness, peripheral edema, weight gain, blurred vision
Gabapentin	Start at 100 mg at bedtime; increase by 100 mg every 2 to 4 weeks to 1,200–2,400 mg daily (usually in 2 or 3 divided doses) as tolerated[46]	As above

- Physical activity and self-management education program for persons with arthritis from the Centers for Disease Control and Prevention(www.cdc.gov/arthritis/programs)
- Pilates for persons with fibromyalgia (youtube.com/watch?v=PnKbwr5WuTw)
- *The FibroManual: A Complete Fibromyalgia Treatment Guide for You and Your Doctor* by Ginevra Liptan, MD (Ballantine Books, 2016)

Water therapy program

- Exercise and aquatic therapy videos from the Aquatic Exercise Association (aeawave.org/Arthritis/At-Home-Exercise-for-Arthritis)

Tai chi programs

- American Tai Chi and Qigong Association (amtaichi.org/tai-chi-qigong-classes-near-you)
- Tai chi for arthritis video lessons by Dr. Paul Lam (youtube.com/watch?v=tAOuEpa01j4)
- Tai chi health benefits (health.clevelandclinic.org/the-health-benefits-of-tai-chi)

Cognitive behavioral therapy

- Online cognitive behavioral therapy program; a referral is required and there is a fee to enroll (thiswayup.org.au/programs/chronic-pain-program)
- Society of Clinical Psychology cognitive behavioral therapy for fibromyalgia (div12.org/treatment/multi-component-cognitive-behavioral-therapy-for-fibromyalgia)
- Pacing resource from the Department of Health, Western Australia (painhealth.csse.uwa.edu.au/pain-module/pacing-and-goal-setting)
- Patient-perspective video about fibromyalgia and successful pain management (youtube.com/watch?v=tFDsdByqkM0)
- Cognitive restructuring (concordia.ca/cunews/offices/provost/health/topics/stress-management/cognitive-restructuring-examples.html)
- Psychodynamic therapy (psychologytoday.com/us/therapy-types/psychodynamic-therapy)
- Cognitive behavioral therapy for insomnia (sleepfoundation.org/insomnia/treatment/cognitive-behavioral-therapy-insomnia)

- Managing insomnia for those with chronic pain (health.clevelandclinic.org/managing-insomnia-for-those-with-chronic-pain)

University of Michigan pain guide

- Chronic pain management (painguide.com/pain-care)
- Self-care videos (painguide.com/pain-care/self-care)
- Cognitive behavioral therapy (painguide.com/pain-care/professional-care/therapies/cbt)
- Acupuncture (painguide.com/pain-care/professional-care/therapies/acupuncture)
- Acceptance and commitment therapy (painguide.com/pain-care/professional-care/therapies/act)
- Tai chi (painguide.com/pain-care/professional-care/therapies/tai-chi)
- Yoga (painguide.com/pain-care/professional-care/therapies/yoga)
- Massage and spa therapy (painguide.com/pain-care/professional-care/therapies/massage-spa)
- Emotional awareness and expression therapy (painguide.com/pain-care/professional-care/therapies/eaet)

Mindfulness

- American Mindfulness Association (goamra.org)
- Mindfulness for chronic pain from Extension Utah State University (extension.usu.edu/heart/files/mindfulnessforchronicpainmanagement.pdf)
- Mindfulness tips from Cleveland Clinic (health.clevelandclinic.org/what-is-mindfulness)
- Breathing, body scan, and compassion exercises (livinginthegap.org/blog/3-mindfulness-activities-to-use-in-your-new-daily-practice)
- Mindfulness exercises from the Mayo Clinic (mayoclinic.org/healthy-lifestyle/consumer-health/in-depth/mindfulness-exercises/art-20046356)
- *Pain: Considering Complementary Approaches* eBook from the National Institutes of Health (nccih.nih.gov/health/pain-considering-complementary-approaches-ebook)

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Psychedelics, spirituality, and existential distress in patients at the end of life

ABSTRACT

Psychedelic-assisted therapy clinical trials conducted over the past decade have prompted increased interest in the use of psychedelics to treat nonphysical suffering, which can include significant spiritual and existential distress at the end of life. The authors explore the role of psychedelics in helping to address patients' spiritual and existential suffering from a medical, ethical, and legal perspective, with the aim of stimulating discussion and research on this timely and clinically promising topic.

KEY POINTS

There is a promising overall body of evidence supporting the use of psychedelic-assisted therapies for alleviating existential distress and improving spiritual well-being at the end of life.

There is a distinction between supervised medical use vs nonprescribed use of psychedelics, specifically regarding patient safety and documented clinical outcomes.

When considering whether psychedelics can be justified as part of end-of-life care, physicians should consider not only the laws in their city and state but also the ethical merits of such advocacy. The principle of proportionate reason, for example, can be useful to that end.

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Existential distress at the end of life in individuals with a terminal illness refers to an inability to find sources of hope, value, meaning, love, strength, and connection.[1] Psychedelic-assisted therapy holds promise for treating end-of-life existential distress,[2,3] but further evidence is needed. At the same time, nonprescription use of psychedelics (including ketamine, 3,4-methylenedioxymethamphetamine [MDMA], psilocybin, and lysergic acid diethylamide [LSD]), along with access to these drugs, continues to grow, even though they remain illegal in most regions of the United States. These factors together can create ethical dilemmas for physicians caring for patients with existential distress at the end of life. This review discusses the role of psychedelics with respect to patients' spiritual and existential suffering at end of life from a medical, ethical, and legal perspective in the context of a fictional case example.

Mark is 45 years old and was given a diagnosis of stage 4 colon cancer a year ago. He has undergone multiple courses of chemotherapy and surgical procedures; however, the cancer continues to spread. Mark is married with 2 young children and works remotely as a social worker. He has no siblings and is estranged from his parents. He has employer-sponsored health insurance. Mark feels a deep sense of hopelessness and anxiety that he is a burden to his family, and that he won't be able to see his children grow up. At his most recent appointment with his oncologist, Mark expresses an interest in using psychedelics to help with his anxiety

and fear. He says that he is spiritual, but not religious, and that he experimented with psychedelics for spiritual purposes during previous trips to Mexican ruins.

As Mark begins to accept the reality of his prognosis, he wonders aloud to his oncologist whether using psychedelics during this time might help him to connect more deeply with his spirituality.

NONPRESCRIPTION USE OF PSYCHEDELICS IS GROWING

Nonprescribed use of psychedelics among the public has been growing over the past decades. In the United States between 2008 and 2019, past-year use of nonprescribed psychedelics ranged from a low of 0.4% to a high of 1.4%, and increased to 4.1% in 2022 among those age 35 to 50.[4] For those age 19 to 30, past-year use of nonprescribed psychedelics ranged from a low of 3.4% to a high of 5.3% between 2008 and 2019 and increased to 8% in 2022.[4] In addition, perceived risk of psychedelics is dropping in the United States, which is likely contributing to increased use.[5] Notably, evidence shows that the prevalence of nonprescribed psychedelic drug use is higher in people experiencing depression than in those not experiencing depression.[6]

UTILITY OF PSYCHEDELICS FOR TREATING MENTAL HEALTH DISORDERS

The use of psychedelics in the treatment of depression, anxiety, and posttraumatic stress disorder (PTSD) has been the focus of a small but growing body of research.

Ketamine

Ketamine was approved by the US Food and Drug Administration (FDA) in 1970 as an anesthetic. Since then, evidence supporting the use of intravenous ketamine as an off-label treatment for both treatment-resistant depression[7] and suicidality[8] has been published. The strength of the evidence has reached a sufficient threshold for the Department of Veterans Affairs and Department of Defense clinical practice guidelines to recommend intravenous ketamine as a treatment for treatment-resistant depression (as of 2022)[9] and suicidality (as of 2019).[10] However, an ongoing challenge has stemmed, in part, from the emergence of commercial practices that prescribe sublingual ketamine via telehealth to patients at home without medical monitoring during ketamine administration and with only minimal therapeutic support from a nonmedical "guide."[11] Although this approach may increase access to ketamine, it is not supported by a large body of evidence from clinical trials.

MDMA

MDMA-assisted therapy has been studied primarily for the treatment of PTSD. Findings from phase 2 studies supported its efficacy and tolerability,[12] and MDMA-assisted therapy was designated as a breakthrough therapy for PTSD by the FDA in 2017. (Note that the Mithoefer et al[12] article was retracted due to unethical conduct by researchers associated with the study.) However, after 2 successful multisite phase 3 clinical trials,[13,14] the FDA in 2024 denied approval of a New Drug Application for MDMA.

Both phase 3 studies found MDMA-assisted therapy to be safe and efficacious for PTSD, with 67% to 71% of participants no longer being diagnosable with PTSD, compared with 32% to 48% in the placebo-assisted therapy group.[13,14] The between-group effect sizes were 0.70 and 0.91, respectively, and the within-group pre- vs posttreatment effect sizes were 1.95 and 2.10, respectively. Current first-line treatments for PTSD such as prolonged exposure and cognitive processing therapy have a reported within-group effect size of 0.78 to 1.10, respectively.[15] Treatment effects were durable both at 1 year[16] and nearly 4 years[17] after completing a course of MDMA-assisted therapy. (Jerome et al[16] also was retracted due to unethical conduct by researchers.)

Psilocybin

Psilocybin-assisted therapy has been studied primarily for the treatment of depression. The FDA designated psilocybin-assisted therapy as a breakthrough therapy for treatment-resistant depression in 2018 and major depressive disorder in 2019. Results from the largest multisite phase 2 trials of psilocybin-assisted therapy for treatment-resistant depression[18] and major depressive disorder[19] have been promising. A breakthrough therapy designation was given to Cybin's psilocybin (CYB003) for major depressive disorder in 2024.[20] Phase 3 trials are now underway, and if they are successful, FDA approval may be anticipated between 2026 and 2027.

One of the first clinical trials that evaluated psilocybin-assisted therapy as a treatment was a 2011 pilot study of 12 adults with anxiety and advanced-stage cancer.[2] A subsequent 2016 study of psilocybin-assisted therapy for the treatment of anxiety and depression in 29 adults with life-threatening cancer found improvements in depression, anxiety, spiritual well-being, quality of life, and cancer-related demoralization and hopelessness 7 weeks after treatment.[3] Effects were durable 6.5 months[3] and 4.5 years after treatment.[21]

LSD

Clinical trials of LSD prior to 1970 primarily looked at the agent's use in the treatment of alcohol use disorder,[22] but more recent LSD-assisted therapy clinical trials have focused on the treatment of anxiety. A 2014 pilot study of 12 participants with anxiety associated with life-threatening illness treated with LSD-assisted therapy found statistically significant improvements in anxiety at 2 months after treatment, and effects were durable after 12 months.[23] As a secondary outcome, the effect of LSD-assisted therapy on depression was not analyzed for statistical significance, but results mirrored the anxiety results. A 2023 study of 42 participants, 48% of whom had a life-threatening illness, found LSD-assisted therapy to be efficacious for anxiety 16 weeks after treatment.[24] Reductions in secondary outcomes of depression were also significant.

EXISTENTIAL DISTRESS AT END OF LIFE

Palliative care, a specialty born out of the hospice movement founded by Dame Cicely Saunders in 1967, aims to alleviate serious illness-related suffering and improve quality of life for patients, caregivers, and loved ones.[1,25,26] Palliative care can be provided at any stage of a patient's life-limiting or life-threatening illness or injury. Hospice is a subset of palliative care intended for patients of any age who have a life expectancy of less than 6 months and are no longer pursuing life-prolonging therapies. Palliative care can be delivered alongside disease-modifying therapies and is tailored to the unique and dynamic needs of patients and families. The most common conditions in which palliative care is involved include cancer, cardiac and vascular conditions, respiratory diseases, dementia, and stroke.[25]

Beyond the physical: The concept of total pain

Central to the foundations of palliative care is Dame Cicely Saunders' concept of "total pain," which proposes that the experience of pain is multidimensional, encompassing physical, emotional, social, psychological, spiritual, and existential dimensions.[1,26,27] Cassel[28] further conceptualized suffering as "the state of severe distress associated with events that threaten the intactness of the person." Palliative care focuses on care of the "whole person" by tailoring interventions to each person's unique history, experiences, values, beliefs, hopes, losses, worries, and fears.[1]

Nonphysical suffering includes emotional, psychological, social, spiritual, and existential domains.[28] Within the palliative care literature, the terms *existential* and *spiritual* suffering are sometimes used interchangeably, and other times their definitions encompass parts of each other or they are even defined as distinct entities.

Deeper sources of suffering: The concept of existential distress

In 2009, a consensus conference was held to formulate recommendations for advancing the delivery of quality spiritual care in palliative care.[29] Conference participants, which included physicians, nurses, and members of the clergy, defined spirituality as the "aspect of humanity that refers to the way individuals seek and express meaning and purpose and the way they experience their connectedness to the moment, to self, to others, to nature, and to the significant or sacred."[29] One's personal spirituality can be inclusive or exclusive of organized religion or faith-based communities of practice. Using this definition, all humans have a spiritual dimension, and spiritual suffering holistically describes challenges to these held beliefs, life and afterlife philosophies, sense of transcendence, religious or nonreligious worldviews, and connection to the self, others, and the sacred or divine.[30]

Identification of spiritual and existential distress hinges on a clinician's ability to develop authentic, empathetic, trusting relationships with patients and families, as well as an understanding of the subjective and personal nature of an individual's expression of nonphysical suffering. Compassion, listening, presence, exploration, and bearing witness are necessary, but may not be sufficient interventions to address these deeper sources of suffering.

MITIGATING EXISTENTIAL DISTRESS WITH TOOLS THAT INCLUDE PSYCHEDELIC-ASSISTED THERAPY

A small study of the attitudes of palliative care healthcare professionals toward existential distress and treatment with psychedelic-assisted therapies revealed 4 major themes[31]:

- Existential distress is common and frequently undertreated
- Existential distress has historically evaded medicalized approaches
- Psychedelic-assisted therapies hold promise for treating existential distress, but stronger evidence is needed
- Psychedelic-assisted therapies do not clearly fit into current treatment paradigms.

A review of tools used to mitigate end-of-life existential distress outlined 4 current psychotherapeutic interventions.[32]

Dignity therapy is a guided interview process that reviews life history and how people want to be remembered, with goals of highlighting meaning, purpose, and legacy.

Managing cancer and living meaningfully (CALM) is a multisession psychotherapeutic intervention designed to build therapeutic relationship, create reflective space, explore changes in physical and nonphysical well-being, explore life's purpose, and address mortality concerns.

Logotherapy is a psychotherapeutic model founded by Holocaust survivor Viktor Frankl, who often quoted Friedrich Nietzsche's observation that "He who has a *why* to live for can bear almost any *how*." Sessions (individual, group, or both) aim to help people find greater meaning in their lives, agency in choosing how to respond in thought and behavior to challenges, and motivation for change and growth.

Reorientation existential therapy involves group sessions based upon meaning-making psychotherapy and cognitive analytic therapy. The sessions emphasize significant life events and interpersonal relationships, culminating in a "goodbye letter" with intended themes of "togetherness and gratitude," "legacy," and "acceptance."

There is consensus in the palliative care community that, when there is time, interest, accessibility, and patient–intervention "fit," offering nonpharmacologic therapeutic interventions, such as these, is the preferred first-line approach to severe spiritual and existential distress.[33] This, of course, is in addition to care provided by appropriate palliative care interdisciplinary team members, such as chaplains for spiritual distress and social workers for psychosocial distress.

Role of psychedelic-assisted therapy

Psychedelic-assisted therapy may appeal to patients who are comfortable with hallucinogens and have no contraindications, such as psychoses. Notably, in the previously described study that looked at psilocybin-assisted therapy for the treatment of anxiety and depression in patients with life-threatening cancer,[3] 70% of participants rated their experience as the singular or top 5 most personally meaningful experiences of their entire lives; 87% reported increased life satisfaction or well-being that they said was a result of the experience. Similarly, between 66% and 86% of individuals who have had a psychedelic experience in a therapeutic setting consider it one of the most spiritually significant experiences of their lives.[34] Furthermore, the intensity of an individual's mystical-type experience is associated with improvements across numerous psychiatric and medical outcome measures.[34,35]

But many questions remain. Beyond questions foundational to understanding the therapeutic applications of psychedelics (eg, dosing, efficacy, adverse effects, safety), there are ethical and legal barriers to the use of psychedelic-assisted therapy as an *existential intervention* in the palliative care population.

LEGAL ISSUES, ETHICAL QUESTIONS AROUND USE OF PSYCHEDELICS

Regulations on both the federal and state levels govern the legal use of psychedelics. Most psychedelics are Schedule I substances, which, by definition, are considered to have no currently accepted medical use and to have a high potential for abuse. Medical research is an exception, as Schedule I substances can be used in clinical trials. The American Medical Association's third principle of medical ethics states that "a physician shall respect the law and also recognize a responsibility to seek changes in those requirements which are contrary to the best interest of the patient."[36] Can a physician then ethically encourage patients to seek illegal psychedelics in nonmedical settings to treat existential suffering at the end of life? A changing regulatory and legal environment around psychedelics is complicating this question.

As noted, the FDA designated MDMA a breakthrough therapy for PTSD in 2017 and psilocybin a breakthrough for treatment-resistant depression in 2018. Breakthrough therapy designation is one of the FDA's expedited drug development pathways. To be eligible for this designation, a sponsor must demonstrate that the investigational product is intended to treat a serious and life-threatening condition, with preliminary evidence supporting a substantial advantage over existing drugs at a clinically significant end point.[37] As phase 2 and 3 psychedelic trials near completion, the FDA may soon approve psychedelic medicines for treating PTSD and treatment-resistant depression. This represents a paradigm shift for the agency, which in 2023 released draft guidance on conducting psychedelic clinical trials.[38] Limited federal funding for psychedelics research has been one of the most important barriers to advancing this work.[39]

In addition, federal agencies are considering changes toward psychedelics, and the US Congress is considering reducing barriers to psychedelic research. These efforts at the federal level include working on passing the Breakthrough Therapies Act (under which substances designated as a "breakthrough therapy" by the FDA would automatically be rescheduled), expanding the use of observational data, reforming the efficacy

requirement, legislatively reclassifying psychedelics, and encouraging policymakers to consider the cost-effectiveness of psychedelic-assisted therapy.[40]

On a local level, more than 7 US cities have passed resolutions regarding psychedelics that vary from decriminalizing certain psychedelic substances to reducing enforcement policies.[41] In addition, in November 2020, Oregon voters legalized the supervised administration of psilocybin, and Colorado voters approved a proposition decriminalizing use of psychedelic mushrooms in November 2022. Eight other states are considering similar legislation to legalize or decriminalize psychedelics.

What is a physician to do?

Given these legal changes, what is the role—and professional obligation—of the physician? In medical ethics, it is understood that physicians have an ethical obligation to promote good and act in the best interest of the patient, as dictated by the physician's moral imperative to find the good and right healing act. What is the right and good healing act in patients suffering from existential distress at the end of life? Do the benefits of using psychedelics to relieve existential suffering at the end of life exceed the risks?

And, in light of the information that is available today, can the physician justify the use of a psychedelic? This question can be explored by using the principle of proportionate reason, which is a moral principle used to determine objectively and concretely the rightness or wrongness of actions by balancing values and disvalues and "determining whether the means (an act) is proportionate to the intended end or reason."[42]

Further, if patients express an interest in seeking out psychedelics on their own, harm-reduction conversations will be necessary. Risks of psychedelic treatments should be discussed with patients, including both common adverse events (eg, nausea, headaches) and rarer but serious adverse events, such as suicidal ideation or behavior, psychosis, and seizures.[43]

Mark returns to his physician's office with increasing symptoms, including pain, depression, and anxiety. He states that he would like to take psychedelics from an online psychedelic medicine "practice." He explains that the current medications to treat his distress have not helped with his suffering and are causing intolerable adverse effects—namely sedation. He has discussed this with his wife, who is very concerned about his emotional state.

After a lengthy discussion and exploration of the meaning of his suffering, as well as the risks of psychedelics, his physician offers him a referral to a local academic center to enroll in a clinical trial of psychedelic-assisted therapy. His physician emphasizes that he can't make a referral for psychedelic therapy outside of a clinical trial because psychedelics have Schedule I status and currently lack FDA approval for this purpose. The physician also takes a harm-reduction approach and explores the potential risks and benefits of going to an underground psychedelic physician, should Mark seek out this treatment on his own.

After this discussion, Mark identifies a physician who provides underground psychedelic-assisted therapy and chooses to pursue that treatment. Over the course of several months, Mark has several sessions that involve the psychotherapeutic integration of psylocibin by trained facilitators. When asked about his psilocybin experience, he describes a part of his experience:

> *"I was lost and running through a dark forest in a bad thunderstorm, trying to find this loud voice that was calling my name. A voice that caused me internal pain. The trees were geometrical shapes that felt suffocating. This was death. All of a sudden, warmth took over me. The rain stopped. The trees turned into my wife, kids, and my parents, with open arms. They had soft smiles and a tender voice saying, 'All is OK.' I was now not lost and started walking toward the sun as the clouds opened the blue sky."*

Mark describes his psilocybin-induced state as one that developed on his interconnectedness and unity with his spirituality. He says his experience has helped him bring insight into the cause of his existential distress. He indicates that he's met with his parents (with whom he had not connected in 10 years) and has been able to process past childhood trauma. He also reports: "I'm at peace with my illness and not afraid of death anymore."

THE FUTURE OF PSYCHEDELICS

The US market for psychedelics is projected to reach $6.85 billion by 2027,[44] attracting a significant number of for-profit companies and investors. As a result, the use of psychedelics will increase—both recreationally and for medical purposes, including at the end of life. It is imperative that clinicians and nonclinicians alike appreciate the issues surrounding psychedelics and end-of-life care. As such, increased attention to the ethical, legal, and social implications of psychedelic use is needed.

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